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SYMPATHETIC CONTROL OF HUMAN BLOOD VESSELS

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TO

O G EDHOLM

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FOREWORD

The role of the sympathetic nerves in the control of the blood vessels has been the object of investigation of many physiologists from the pioneer work of Gaskell Langley and Elliot in this country In recent years interest in the nature of the chemical transmitter of the sympathetic nerves has widened the topic It appears to us opportune to describe the sympathetic control of certain blood vessels in man and to comment on the function of the sympathetic hormones—adrenaline and noradrenaline

This work has been written primarily on the basis of studies on the circulation in the extremities but we feel that the responses have a more general application to the function and behaviour of blood vessels in other parts of the body We have described certain fundamental experiments in some detail in order to impress their true importance on the reader In many aspects however omissions will be readily evident both in problems still to be solved and in observations of others on this topic But we do not regard a review of the subject as our present task our object is to present the concept of the control of the blood vessels from the view point of the investigator in this special field

It is a great pleasure to acknowledge our gratitude to Dr O G Edholm Director of the Division of Human Physiology of the National Institute for Medical Research who collaborated with one of us in the work described in the early chapters Without his wise counsel and outstanding experimental skill this book would never have been written

The investigations on sympathectomized subjects were made possible by the kindness of Mr Hedley Atkins Miss Diana Beck Mr P Fitzgerald Mr Ian Frazer Mr J B Kinmonth Professor Sir James Learmonth Mr J S Loughridge Mr Peter Martin Mr D W C Northfield the late Mr G R B Purce Professor C G Rob and Sir James Paterson Ross The experiments on fainting were begun with Professor J McMichael and Professor E P Sharpey Schafer To all of these we express our deepest gratitude

Once more we should like to thank all those who have given

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We are grateful to Professor W G Barnard Dean of St Thomas s Hospital Medical School for the provision of many facilities to the St Thomas s Hospital Endowment Fund for a grant towards the expenses of one of us and to the Medical Research Council for financial assistance

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For permission to quote passages or reproduce figures from books and journals we express our thanks to the following *American Journal of Physiology* Fig 7 6 top left and right Association for Research in Nervous and Mental Diseases Fig 7 11 *British Medical Journal* Fig 11 2 Cambridge University Press quotation from Foster s Lectures on the History of Physiology *Clinical Science* Figs 4 1 4 3 and 7 5 *Heart* Fig Ap 4 *Journal of Physiology* quotation from Brodie and Russell s article and Figs 1 2 2 1 2 2 2 3 3 2 3 4 3 5 3 7 3 8 3 9 4 2 5 5 5 6 5 7 6 3 6 4 6 5 7 7 8 1 8 2 8 3 9 3 10 1 10 3 10 4 and 12 3 *Lancet* Figs 7 8 7 9 7 10 10 6 *12 1 and 12 2 Zeitschrift für Kreislaufforschung* Figs *12 4 and* 12 5 Macmillan Fig 12 2 (and legend) *Pflügers Archiv* Fig 5 10 *St Thomas s Hospital Reports* 7 2 7 3 and 7 4 *Surgery Gynecology and Obstetrics* Fig Ap 1 (and legend) In each instance the author of the article from which the figure was borrowed has been mentioned in the legend

Finally we are most grateful to the Editorial Committee of the Physiological Society for sponsoring the publication of this book

H B
H J C S

6th August 1952

CONTENTS

CHAPTER 1

SYMPATHETIC VASOCONSTRICTOR NERVES TO SKELETAL MUSCLE

In 1941 W McKee Bonnar obtained the M D of the Queen s University of Belfast with Gold Medal for a thesis entitled The action of the sympathetic on the blood vessels of human skeletal muscle In this chapter with special reference to Bonnar s thesis some evidence will be given that the blood vessels of human skeletal muscle are supplied by sympathetic vasoconstrictor fibres and subjected to nervous vasoconstrictor tone

At the time the work was done a great deal was known about the action of the sympathetic on the blood vessels in the muscles of animals Section was generally followed by vasodilatation due to release of constrictor tone strong stimulation caused vasoconstriction or weak vasodilation (Baetjer 1930 Burn 1932 Gilding 1932 Anrep Blalock and Samaan 1934 Bulbring and Burn 1935 1937) Vasoconstrictor fibres were found in the muscles of all animals examined but vasodilator fibres in some species only (Bulbring and Burn) Very little was known about the sympathetic innervation of the vessels of human muscles Some thought that it was constrictor and advised sympathectomy for intermittent claudication others believed that it was dilator (Finch 1944) and others considered it to be of very little significance (Abramson Zazeela Marrus 1939 Grant and Holling 1938 Prinzmetal and Wilson 1936 Woollard and Phillips 1932) It was not concerned with vasodilatation in exercise which was caused by metabolites (Grant 1938)

Barcroft Bonnar Edholm and Effron (1943) noticed that warming the body caused a conspicuous increase in the blood flow in a very muscular part of the body the forearm (Fig 1 1 top plethysmographic method see Appendix) This was of nervous origin mediated by the sympathetic since it was abolished by sympathectomy (Fig 1 1 bottom left) It occurred after adrenaline had been introduced into the

forearm skin by electrophoresis to suppress the circulation (Fig 1 1 bottom right Fig 1 2) To see if it was due to the release of sympathetic vasoconstrictor tone in the muscles the median radial and ulnar nerves the motor nerves of the forearm which would be expected to convey any sympathetic fibres to the muscles (Gilding 1932) were blocked by novocaine

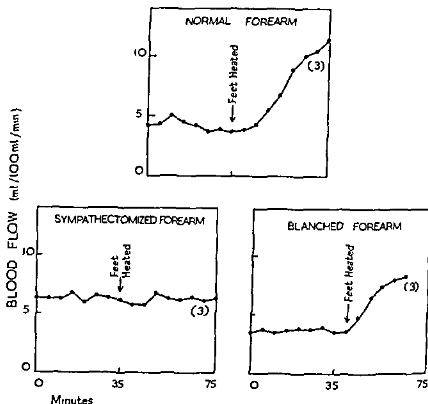


Fig 1 1 Experiments showing sympathetic control of the blood vessels in *human skeletal muscle*

Top Vasodilatation in the forearm after immersing the feet in warm water

Bottom right It can be induced when the skin vessels are strongly constricted by adrenaline (introduced by electrophoresis) It is probably in the skin in the skeletal muscles which make up 60 per cent of the forearm tissue

Bottom left The vasodilatation abolished by sympathectomy It is mediated by sympathetic fibres supplying blood vessels which are probably in the skeletal muscles

Averaged results Number of subjects in brackets ... water bath temperature 3 C

Fig. 1. Photograph showing intense [illegible] of the minute vessels of a large area of skin [illegible] by [illegible]. After electrophoresis the circulation was arrested for a few minutes. The photograph was taken a short time after release when there was [illegible] reactive hyperaemia [illegible] the skin [illegible] had [illegible] skin [illegible] with [illegible] a white piece of cardboard. [illegible] (Barcroft, Bonnar, Edholm and Effron, 1943.)

on one side of the body (Fig 1 3) and the circulation in the two forearms was compared The blood flow was approximately doubled on the side of the nerve blocks (Figs 1 4 and 1 5 Table 1) Before concluding that this hyperaemia was due to release of sympathetic tone in the muscles other possibilities had to be considered

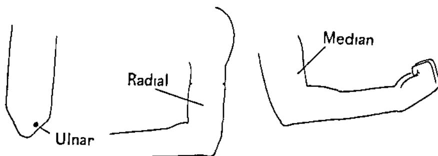


Fig 1 3 Sites for blocking the deep nerves supplying the skeletal muscles of the forearm

(1) The nerve blocks had all been done on the left forearm It was conceivable that the normal circulation on the left side was faster than that on the right Comparison of the blood flows on the two sides showed that the rates are approximately equal (Fig 1 4 top right)

(2) A small area of forearm skin about one third generally became anaesthetized due to unavoidable diffusion of local anaesthetic outwards to the cutaneous nerves The sympathetic supply to this skin must have been blocked and the increase in forearm blood flow might have been due to release of tone in the cutaneous vessels The effect of blocking the

Fig 1 4 Results showing sympathetic vasoconstrictor tone in the vessels in human skeletal muscle

Top left When the deep nerves (containing sympathetic) to the left forearm muscles are blocked the blood flow (circles and broken line) is about double that in the opposite normal forearm (dots and continuous line)

Top right This is not due to any inherent difference in the vascularity of the two sides (control 1)

Middle Or to unavoidable blocking of the sympathetic supply to ⅓ of the forearm skin (control 2)

Bottom left Or to removal of the mechanical hindrance of the tonic contraction of the skeletal muscles (control 3)

Bottom right Or to passive increase in flow through the forearm skin following release of vasomotor tone deep in the arterial tree (control 4)

Conclusion It must be due to the release of sympathetic vasoconstrictor tone in the blood vessels which are probably in the skeletal muscles

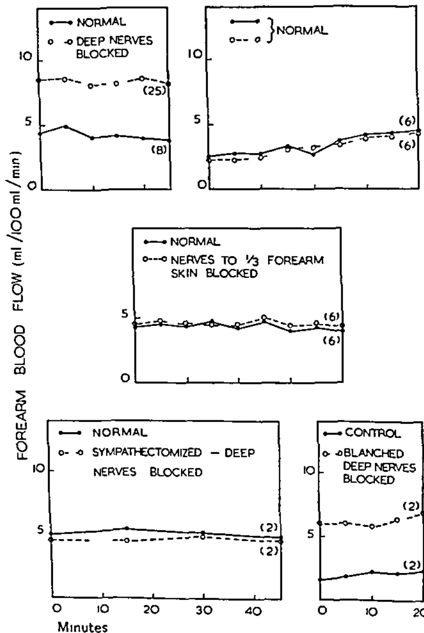

NORMAL
DEEP NERVES BLOCKED
(25)
(8)
NORMAL
(6)
(6)
NORMAL
NERVES TO 1/3 FOREARM SKIN BLOCKED
(6)
(6)
FOREARM BLOOD FLOW (ml/100ml/min)
NORMAL
SYMPATHECTOMIZED — DEEP NERVES BLOCKED
(2)
(2)
CONTROL
BLANCHED DEEP NERVES BLOCKED
(2)
(2)
Minutes

Fig 14

cutaneous nerves of the forearm on the forearm circulation was therefore tested (radial median and ulnar antebrachial nerves localized by the method of Trotter and Davies (1909)) and found to increase the forearm blood flow on the average by

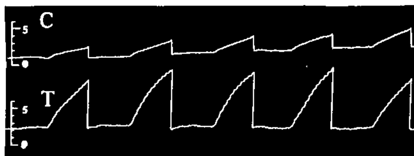


Fig 1 5 Simultaneous records of blood flow in the normal forearm (C) and in the opposite forearm in which the deep nerves were blocked (*T*) The rate of the blood flow in the nerve blocked forearm is increased owing to the release of tone in the muscle blood vessels

Recorded at the Cambridge meeting of the Physiological Society Oct 1941 Temperature of plethysmograph waterbath 3[illegible] C Calibration in millilitres No time tracing was made

TABLE I

Subject	Blood flow ml per 100 ml forearm per min		Difference	Percentage difference
	Right	Left	L − R	$\frac{L-R}{R} \times 100$
H B	6 9	10 3	+3 4	+49
W B	4 1	6 [illegible]	+2 1	[illegible]1
H B	4 4	8 [illegible]	[illegible]4 3	+9[illegible]
J S L	4 0	8 1	[illegible]4 1	+103
D C H	1 8	4 [illegible]	+2 9	+161
W B	2 0	[illegible]9	−3 9	+19[illegible]
A S F	3 [illegible]	9 8	[illegible]6 6	+206
Average	3 8	[illegible]	+3 9	+105

24 per cent Anaesthesia of one third of the forearm skin would have increased the flow by only 8 per cent (Fig 1 4 middle) This could not explain the far greater increase in flow found after blocking the deep nerves (10[illegible] per cent)

(3) Blocking the deep nerves paralysed the forearm muscles

Conceivably the hyperaemia was due to abolition of muscular tone and decrease of mechanical hindrance to the circulation However similar blocks performed on sympathectomized limbs did not increase the flow (Fig 1 4 bottom left)

(4) Claude Bernard (1876) observed a rise of 25-60 mm Hg in the central end of the labial artery of the horse following section of the cervical sympathetic Conceivably the hyper aemia in the forearm after deep nerve block was caused by release of tone in the arterial tree beneath the deep fascia and passive increase in the cutaneous circulation This was tested by observing the effect of deep nerve block on the forearm circulation after blanching the skin with adrenaline Table II

TABLE II

Protocol

Subject O C L Lying on couch Plethysmograph diaphragms fitted to both forearms but plethysmograph not put on till later

Time in Minutes	
0–15	Rest Forearms kept warm under blankets
15–20	Cottonwool pad bandaged round both forearms between the diaphragms Electrode put on each pad Left pad soaked in adrenaline solution at room temperature right one soaked in saline at the same temperature
20–30	Electrophoresis
33–35	Pads off 95% of skin of left forearm intensely blanched with marked gooseflesh
35–40	Deep nerves blocked in the left forearm (blanched)
40–45	Plethysmographs put on Wrist cuffs put on (till 60th min) and inflated to 200 mm Hg to prevent blood from the hands from affecting the temperature of the forearms
45–53	Blood flows recorded simultaneously in both forearms at 2 min intervals 6 sets obtained for averaging Results left forearm (blanched deep nerves blocked) 2 1 ml right forearm (normal) 0 4 ml
53–55	Motor movements tested Complete paralysis of those mediated by the radial and ulnar nerves Weakening of those mediated by the median
55–60	Calibration
60–61	Cuffs and plethysmographs taken off Intense blanching of skin on left side
61–64	Circulation in both forearms arrested for 5 min After release flushing of the skin of the right forearm and of the left above and below but not in the blanched area
7- 74	Skin temperatures taken Left forearm (blanched deep nerves blocked) 26 9 C Right forearm (normal) 29 1 C In accordance with reduction of the cutaneous blood flow on the left side

is the protocol of a typical experiment Fig 1 4 (bottom right) shows the results The blood flow was small because the fore arms were cooled to make the blanching more effective The important point is that it was trebled in the blanched forearm in which the deep nerves had been blocked Control experi ments showed that adrenaline alone caused constriction The vasodilatation must have been caused by the nerve blocks and it could not have been in the skin

The whole series of experiments may be summarized as follows —After deep nerve block the blood flow in the left forearm is about double that in the right This is not due to an inherent difference in the vascularity of the two sides (control 1) or to release of vasoconstrictor tone in the skin (control 2) or to the removal of the mechanical hindrance of tonic muscular contraction (control 3) or to a passive increase in flow through the forearm skin following release of tone deep in the arterial tree (control 4) It must be due to the release of sympathetic vasoconstrictor tone in the blood vessels in the skeletal muscles

REFERENCES

Abramson D I Zazeela H and Marcus J (1939) *Amer Heart J* **17** 206

Anrep G V Blalock A and Samaan A (1934) *Proc roy Soc B* **114** 223

Baetjer A M (1930) *Amer J Physiol* **93** 41

Barcroft H and Edholm O G (1943) *J Physiol* **102** 5

Barcroft H Bonnar W McK Edholm O G and Effron A S (1943) *J Physiol* **102** 21

Bernard C (1876) *Leçons sur la chaleur animale* Paris Baillière

Bonnar W McK (1941) M D Thesis Queen's University Belfast

Bulbring E and Burn J H (1935) *J Physiol* **83** 483

—— (1937) *J Physiol* **88** 341

Burn J H (1932) *J Physiol* **75** 144

Finch E I (1944) *Surgery of Modern Warfare 3rd Edn* Ed Bailey Edinburgh Livingstone

Golding H I (1932) *J Physiol* **74** 34

Grant R T (1938) *Clin Sci* **3** 157

Grant R T and Holling H E (1938) *Clin Sci* **3** 273

Grinzmetal M and Wilson C (1936) *J clin Invest* **15** 63

Trotter W and Davies H M (1909) *J Physiol* **38** 134

Woollard H H and Phillips R (1932) *J Anat Lond* **67** 18

CHAPTER 2

SYMPATHETIC VASODILATOR NERVES TO SKELETAL MUSCLE

The discovery of sympathetic vasodilator fibres to human muscle vessels was made accidentally during the war at the British Postgraduate Medical School (Barcroft Edholm McMichael Sharpey Schafer 1944) During an experiment on haemorrhage one of the subjects (a Friends Ambulance Unit volunteer) fainted and the tracing of the forearm blood flow shown in Fig 2 1 was recorded The faint began soon after the twentieth minute and was fully developed by the twenty fifth The increase in the forearm blood flow during the faint was unexpected for Lewis (1932) and Wallace and Sharpey Schafer (1941) had shown that the arterial blood pressure falls precipitously The increase must therefore have been due to decreased vascular tone The circulatory changes in 9 faints are shown in Fig 2 2 and the averaged blood flow results in Fig 2 3 (top left) They leave no doubt of the increase in fore arm blood flow or of the decrease in the tone of the forearm vessels

Whereabouts in the forearm was the decrease in tone? It was unlikely to be in the skin—the face went deadly pale—or in the relatively avascular bones and was probably in the muscles which make up the bulk of the forearm tissue (Abramson and Ferris 1940) This was confirmed by the observation

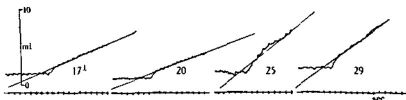
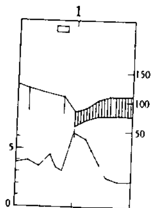
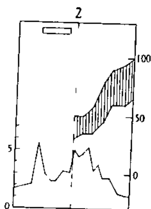
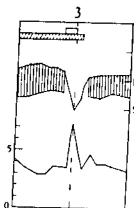


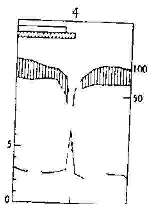
Fig 2 1 Plethysmographic tracings of the forearm blood flow recorded by Dr O C Edholm during the first experiment on posthaemorrhagic fainting They show the increase in flow during the faint

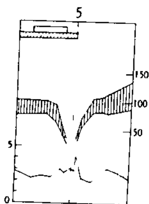
Fainting began soon after the 20th minute and was fully developed at the 25th minute Further details of the experiment are shown in Fig 2 2 No 1 (Barcroft and Edholm 1945)

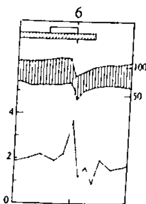

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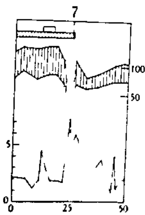

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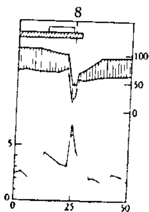

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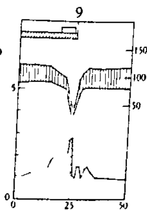

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that during the faint the blood flow through the hand which contains only a small amount of muscle decreased (Fig 2 3 top right) (Barcroft and Edholm 1945)

It was now necessary to find out if possible the cause of the vasodilatation Was it nervous or hormonal ? It might have been due to the vasomotor centre (Chapter 1) or to the action of adrenaline for Grant and Pearson (1938) had shown that small doses of adrenaline caused vasodilatation in human muscle This could be decided by experiments on sympathectomized subjects If the vasodilatation did not occur during the faint in sympathectomized subjects it would be because the vasomotor centre could not dilate the muscle vessels If it did occur it would be due to the action of a hormone

The results of the experiments on the sympathectomized subjects are shown in Fig 2 3 (bottom left) During the faint forearm blood flow decreased the increase recorded in the forearms of normal subjects must have been due to the action of the vasomotor centre

Was the increased rate of blood flow due to release of tone in the muscle vessels or to the excitation of active vasodilatation as well ? This might be settled by comparing the blood flow in normal and recently sympathectomized forearms during the faint If it was greater in the normal one there must be active vasodilatation as well as release of constrictor tone It would not be possible to use for this comparison the results obtained on the sympathectomized patients Owing to the return of tone in the first few weeks after operation (see Chapter 7) the blood flow in their limbs would be far less than that in freshly sympathectomized ones Normal forearms would have to be used in which the pathway from the vasomotor centre to the vessels was acutely interrupted by nerve blocks (see Chapter 1)

Fig 2 3 (bottom right) shows the results obtained in subjects

Fig [illegible] Experiments showing that vasodilatation takes place in the forearm during induced p[illegible] th[illegible] mo rhag[illegible] fainting
Sha ted [illegible] e f ngl [illegible] ven [illegible] s to [illegible] n q [illegible] 1 [illegible] n both thighs [illegible] t [illegible] trap about 700 ml [illegible] blood in the leg (Barcroft et al 1940)
Pla[illegible] tangl[illegible] ven se t[illegible] n [illegible] B [illegible] ke [illegible] verti al l ne faint f lly d vel ped Upp[illegible] r[illegible] [illegible] a te al [illegible] l d pres [illegible] re [illegible] mm Hg Lower c[illegible] ve [illegible] Blood fl w [illegible] th[illegible] n rmal forearm ml 100 ml f rea [illegible] m[illegible] n T me in m n t[illegible] (Barcr ft and Edholm 194[illegible])

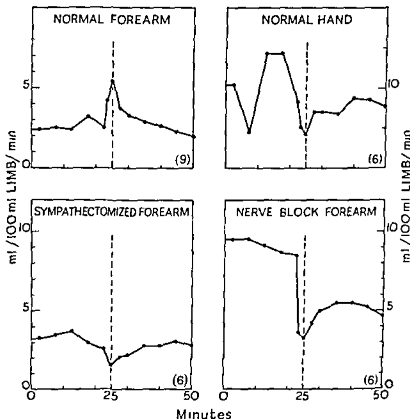


Fig. [illegible]3 Results showing that the vasodilatation in the forearm during induced posthaemorrhagic fainting is mediated by the sympathetic innervation of the skeletal muscle vessels.

Broken vertical line: faint fully developed.

Top left: Increase in blood flow in the normal forearm during fainting. Averaged results of experiments shown in Fig. [illegible].

Top right: Decrease in flow in the hand during fainting. The increase in flow in the forearm (top left) is therefore probably in the skeletal muscles.

Bottom left: Decrease in flow in the sympathectomized forearm during fainting. The increase in flow in the normal forearm (top left) must be due to the action of the sympathetic innervation of the skeletal muscle vessels.

Bottom right: Decrease in blood flow in the forearm during fainting after acute denervation of the muscles by nerve block. The results shown in this figure were used to decide whether the increase in flow in normal forearms is due merely to the release of sympathetic vasoconstrictor tone or in addition to active vasodilatation excited by sympathetic vasodilator fibres. For further details see Fig. [illegible]4.

Averaged results. Number of subjects in brackets. (Barcroft and Edholm, 194[illegible].)

fainted after deep nerve blocks There was a large resting blood flow due to the release of vasoconstrictor tone During the faint the flow decreased passively with the fall in arterial blood pressure The results obtained on the normal forearms (Fig 2 3 top left) and in the forearms after deep nerve blocks

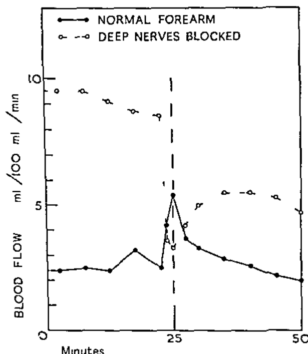


Fig 2 4 Results showing that the blood vessels in human muscle are supplied with sympathetic vasodilator fibres

In this figure the results seen in Fig 2 3 (top left and bottom right) have been superimposed

When the faint was fully developed (broken vertical line) the blood flow in the normal forearm was considerably the greater This is probably explained by active vasodilatation in the normal forearm excited by sympathetic vasodilator fibres

(Fig 2 3 bottom right) are shown superimposed in Fig 2 4 When the faint was fully developed the blood flow in the normal forearms was considerably greater than that in the nerve blocked forearms This must have been due to active vaso dilatation mediated by sympathetic vasodilator nerve fibres

REFERENCES

Abramson D I and Ferris E B (1940) *Amer Heart J* **19** 541
Barcroft H Bonnar W McK Edholm O G and Effron A S (1943) *J Physiol* **102** 21
Barcroft H and Edholm O G (1945) *J Physiol* **104** 161
Barcroft H Edholm O G McMichael J and Sharpey Schafer E P (1944) *Lancet* **1** 489
Ebert R V and Stead E A (1940) *J clin Invest* **19** 561
Grant R T and Pearson R S B (1938) *Clin Sci* **3** 119
Lewis T (1932) *Brit med J* **1** 873
Wallace J and Sharpey Schafer E P (1941) *Lancet* **2** 393

CHAPTER 3

THE ACTION OF ADRENALINE ON THE CIRCULATION IN SKELETAL MUSCLE

In the previous chapters we were concerned with the action of sympathetic nerves on the circulation in the skeletal muscles. It is convenient to turn now to the changes caused in the muscle vessels by the action of adrenaline.

The first relevant observations in man were made by Grant and Pearson in 1938. They found, as shown in Fig 3 1, that the intravenous injection of small doses of adrenaline caused a great increase in the calf blood flow as measured with the plethysmograph. However in a later paper not directly concerned with the subject Holling (1939) pointed out that if adrenaline is given as a continuous infusion the dilatation is not maintained.

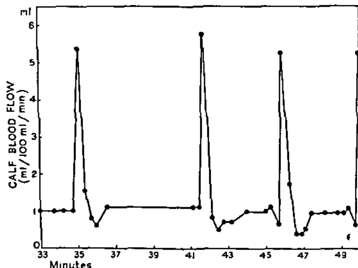


Fig 3 1 Plethysmographic results obtained by Grant and Pearson showing vasodilatation in the calf following each of four successive intravenous injections of 1 µg of adrenaline.
Since adrenaline always caused vasoconstriction in the skin they concluded that it must have a vasodilator action on the blood vessels in the calf muscles. (Grant and Pearson 1938)

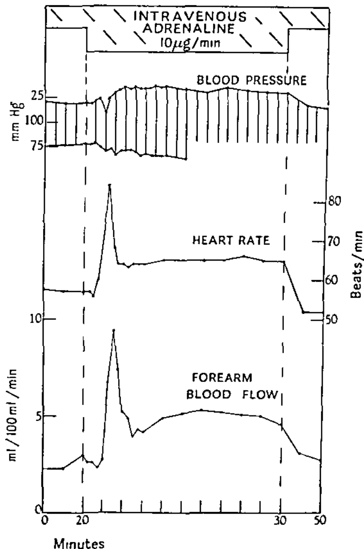


Fig. 3. Results showing that intravenous adrenaline causes a large transient followed by a small sustained vasodilatation in the forearm.
The transient vasodilatation is due to a direct action of adrenaline on skeletal muscle vessels. The sustained one is due to a direct action of some other humoral substance.
Averaged results of experiments on 6 subjects (Allen, Barcroft and Edholm 1946).

Allen Barcroft and Edholm (1946) investigated the problem in some detail also using the plethysmograph They confirmed Holling's finding observing a large transient dilatation in the forearm during intravenous infusions This did not last longer than 2 min after which the flow subsided to about double its initial value Fig 3 2 is taken from their paper

It will be convenient now to follow first the investigations on the cause of the transient vasodilatation and then to pass on to those on the subsequent sustained vasodilatation

The Transient Vasodilatation

The problem which interested Allen et al concerned the nature of the initial transient dilatation *It was not due to* emotional changes for it did not occur in experiments in which the subjects thought they were receiving adrenaline when in fact they were not Also very small doses of adrenaline

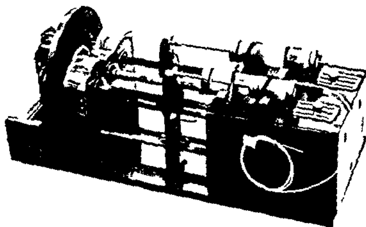


Fig 3 3 Photograph of the infusion apparatus made by P T Machell in the Radiotherapy Workshop St Thomas's Hospital

By alternate use of the syringes a continuous infusion of saline is kept up throughout an experiment at about 4 ml min

As soon as a syringe is nearly empty the adaptor on the tubing leading to the needle is pulled off the nozzle and pushed on the nozzle of the other syringe The empty syringe is then removed refilled and replaced

Adrenaline is added to the saline as and when required (Duff *J Physiol*)

insufficient to cause symptoms frequently caused the transient dilatation without the subjects knowledge

The saline containing the adrenaline could not have caused it for it was infused at a constant rate during the whole of every

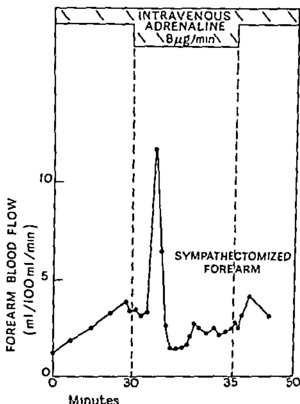


Fig 3 4 Result showing that intravenous adrenaline causes a transient vasodilatation in the sympathectomized forearm

The vasodilatation is not mediated by the sympathetic supply to the skeletal muscle vessel (Allen Barcroft and Edholm 1946)

experiment the adrenaline was merely added to it Fig 3 3 shows an infusion apparatus

The effect could not be a passive one due to increase in arterial blood pressure Careful examination of the records showed that the transient increase in flow often coincided with a transient fall in the blood pressure For a simple increase in pressure to cause the increase in flow the mean arterial pressure would have to exceed 400 mm Hg

Fig 3 2 shows that there was a transient change in the heart rate rather like that in the blood flow Atropine was given to paralyse the vagal nerve endings adrenaline was then infused intravenously as before The transient heart rate change was abolished but the transient vasodilatation persisted They were not cause and effect

Could it have been due to activity of the vasomotor centre ? This seemed unlikely for if the forearm and calf blood flows were measured simultaneously the transient vasodilatation appeared in the forearm before it did in the calf This suggested that the dilatations were due to the local action of adrenaline reaching the forearm first and the calf later To put the matter to a more direct test intravenous infusions of adrenaline were given to subjects who had undergone sympathectomy Fig 3 4 shows a typical result It was clearly not dependent upon the presence of the vasomotor nerves

Finally Allen et al showed that intra arterial adrenaline caused the transient vasodilatation (Fig 3 5) It must have been due to the direct action of adrenaline on the vessels of the limb

The whereabouts of the transient vasodilatation was then considered Since at the beginning of the infusion the skin always paled it was probably in the muscles To test this observations were made on the circulation in the hand which contains relatively much less muscle and relatively much more skin than the forearm (Abramson and Ferris 1940) If the transient dilatation was in the muscles then it would be less conspicuous in the hand than in the forearm If it was in the skin it would be more conspicuous in the hand The results showed that it was much less evident in the hand so the dilatation in the forearm was in the muscle vessels

The possibility that it was due to opening of the vessels in the muscles followed almost immediately by closing of those in the skin was considered and had to be rejected for the following reason Before the beginning of the infusion the cutaneous blood flow could not exceed the total forearm blood flow i e about 3 ml /min (Fig 3 2) Closing the cutaneous vessels could not reduce the flow by more than that amount Yet the decrease in flow immediately after the peak of the initial transient vasodilatation exceeded it and amounted to 5 ml /min (Fig 3 2) Therefore both the initial dilatation

and the subsequent abrupt decrease took place in the same vascular bed i e that in the muscles

There is a certain amount of information relevant to the whereabouts of the vasodilatation in the muscle vessels Dale

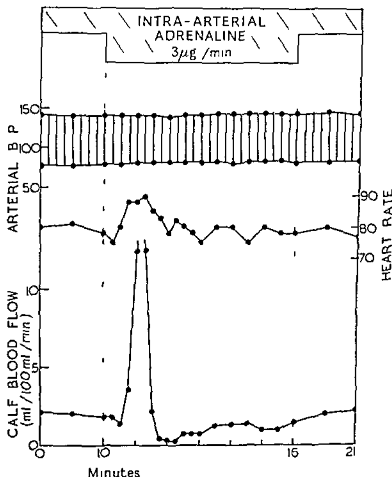


Fig 3 5 Result showing that an intra arterial infusion of adrenaline causes a transient vasodilatation in the calf
The vasodilatation is due to a direct local action of the adrenaline on the skeletal muscle blood vessel (Allen Barcroft and Edholm 1946)

and Richards (1918) concluded from the analogy of their findings with acetylcholine and histamine that adrenaline caused a dilatation of capillaries but a constriction of arterioles Hartman Evans and Walker (1928) confirmed this

An explanation of the transient vasodilatation in man on the basis of capillary vasodilatation followed by arteriolar constriction presents some difficulty For example Fig 3 2 shows that at the beginning of the adrenaline infusion the blood flow increased fourfold That is to say the resistance in the muscle circulation must have decreased to a quarter of its resting amount If this was due to capillary vasodilatation then before the infusion at least three quarters of the total resistance

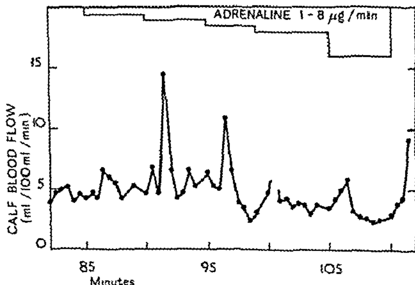


Fig 3 6 Results showing the effect on the calf blood flow of stepwise increase in the intra-arterial infusion of adrenaline from 1 to 8 µg /min
Transient vasodilatation occurred whenever the rate of infusion was increased
During the most rapid infusion after transient vasodilatation there was vasoconstriction

must have been in the capillaries and must have been abolished by the arrival of the adrenaline It is conceivable that this may be so but it has never been demonstrated and seems unlikely

Moreover the explanation of the effect of adrenaline must account for the fact that during a continuous infusion successive increases in its rate cause successive transient vasodilatations as shown in Fig 3 6 (Allen 1946 Stead 1950 Swan 1951) and for the fact that during intravenous infusions at rates ranging

from the minimum to be effective (1 μg / min) to the maximum that can be tolerated without discomfort (20–30 μg /min) both dilator and constrictor phases of the transient dilatation are present the two cannot be dissociated as one would suppose might happen if the adrenaline had independent actions on two distinct parts of the vascular bed

According to Zweifach (1949) the anatomical arrangement of the vessels in skeletal muscles is more complex than is commonly supposed He describes arterio venous anastomoses thoroughfare channels precapillary sphincters and true capillaries If this is confirmed the interpretation of the transient vasodilatation becomes more difficult

It may be that when adrenaline reaches the periphery it causes the momentary liberation of a vasodilator substance from the arterioles which is swept on and causes transient dilatation of the precapillary sphincters Or it may be that it has a dual action on the arterioles—first dilatation and then constriction Many substances have a paradoxical action—that of nicotine on the ganglia is a good example—conceivably while adrenaline begins to pass across the membrane of the smooth muscle cell normal function is temporarily inhibited and vasodilatation occurs and when equilibrium is reached the vessels return to a state of tonus governed by other factors Either of the mechanisms if they existed could explain why successive transient vasodilatations occur in response to successive increases in the rate of a continuous infusion

The fundamental cause of the transient vasodilator action of adrenaline is complex in the extreme and more precise statements on the causation are not at present possible

The Sustained Vasodilatation

At the beginning of this chapter it was shown that intravenous infusion of adrenaline caused a transient vasodilatation in the forearm followed by a smaller sustained one (Fig 3 2) This was confirmed by Duff and Swan (1951 Table III) Similar sustained vasodilatation follows transient vasodilatation in the calf (Duff and Swan 1951 Fig 3 7) The sustained vasodilatation is of singular interest as it probably represents the response of human muscle blood vessels to the natural physiological secretion of the suprarenal glands

TABLE III

Changes ın forearm blood flow ın normal and ın sympathectomized limbs during intravenous infusions of adrenaline and ın normal lımbs during intra arterial infusions of adrenaline Blood flow ın ml /mın /100 ml tissue (Duff and Swan 1951)

No	Age (yr)	Se	Blood fl w A	B	B–A	(B–A)/A %	Blood pressure A	B	Condit on	D
			( ) Norm l forearm ntraven us adrenaln 10 μg /mın							
1	18	M	3 4	5 6	+ 2	+65	128/80	160/65	Normal	—
	19	M	3 4	6 4	+3 0	+88	116 85	140/80	Norm l	—
3	18	M	3 4	7 7	+4 3	+1 7	135 80	165/65	N rm l	—
4	19	M	0	4 6	+ 6	+130	135/80	155/70	Norm l	—
5	19	M	4	3	+0 8	+33	135/80	150/7	Normal	—
6	19	M	1 7	3 9	+2 2	+130	—	—	Norm l	—
7	19	M	3 5	5 4	+1 9	+54	134/80	160 6	Norm l	—
8	33	M	1 9	4 7	+ 8	+147	—	—	N rm l	—
J	33	M	1 8	4 2	+2 4	+133	—	—	N rmal	—
		Av	6	5 1	+2 4	+101 /				
			(b) Symp th tom ed forearm ınt nous adr alın 10 μg /mın							
1		M	3 1	3 9	+0 8	+26	12 /76	140/76	Hype h d osis	6
	43	M	4 0	3 5	−0·5	−13	130/74	156/60	Causalgia	7
3	3	M	4 6	5 5	+0 9	+19	—	—	Hyperhıdros s	1
4	3	F	6	4 4	+1 8	+69	118/9	148/74	Raynaud disease	4
5	29	M	5 9	2	−0 7	−1	110 66	140/64	Causalgı	4
6	29	M	6 7	5 9	−0 8	−1	—	—	Causalgı	4
7		F	5	4 4	+1 9	+76	112/70	140/68	Raynaud disease	18
		Av	4 2	4 7	+0·5	+2 /	—	—	—	—
			( ) Normal forearms ntra arterial adrenalın ½ μg /mın.							
1	21	M	3 0	3 1	+0 1	+3	—	—	Normal	—
	29	M	8 7	3 8	−4 9	−56	—	—	Norm l	—
3	21	M	1 9	1 7	−0	−10	—	—	Normal	—
4	21	M	6 0	6 3	+0·3	+5	—	—	N rm l	—
5	20	M	6 0	7 0	+1 0	+17	—	—	Norm l	—
6	20	M	5 3	6 0	+0 7	+13	—	—	Norm l	—
		Av	5	4 7	−0 5	−5 /	—	—	—	—

A = m n durı g th 4 mı prıo to th start f th adren lıne B = mean d rıng the last 4 mın. of th adre alıne i fusıo D = durat n of ymp thectomy ın months

The explanation of the sustained vasodilatation is still unknown The search for it has been narrowed down by Duff and Swan (1951) and by Whelan (1952)

Arterial hypertension accompanying the intravenous adrenaline does not seem to be responsible Mean pressure is raised by only 10 mm Hg whereas the blood flow in the forearm is doubled In individual experiments the changes in pressure and flow often seem to be quite unrelated

The sustained vasodilatation does not appear to be due to a direct action of adrenaline on the muscle blood vessels Duff and Swan found that during intra arterial infusions of small

amounts of adrenaline the blood flow in the calf and forearm after the initial transient vasodilatation returns to the initial level (calf 1 μg /min forearm ⅛ μg min see Fig 3 7 and Table III) A larger amount (2 μg /min) caused constriction in the calf

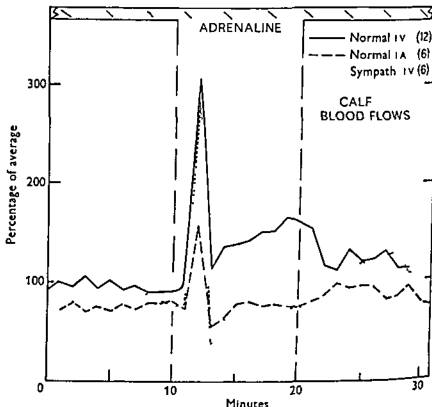


Fig 3 7 Result of experiments on the sustained vasodilatation in muscle caused by intravenous adrenaline

Continuous line Intravenous adrenaline causes transient and sustained vasodilatations in the calf (10 μg /min)

Discontinuous line Intra arterial adrenaline causes transient vasodilatation only The sustained vasodilatation cannot be due to the direct local action of adrenaline on the skeletal muscle vessels (1 μg /min)

Dotted line Intravenous adrenaline causes transient vasodilatation only in chronically sympathectomized limbs (10 μg /min)

In acutely sympathectomized ones however the sustained vasodilatation is present (Fig 3 8)

Averaged results of experiments Number of subjects in brackets (Duff and Swan 1951)

Whelan thought that the failure to find any direct vaso dilator action might have been because the rates of adrenaline infusion were too great For the intra brachial infusions Swan and Duff had used a rate of $\frac{1}{8}$ μg /min Whelan thought that the amount of adrenaline entering the forearm during an intravenous infusion at 10 μg /min would be about $\frac{1}{10}$ μg /min and might be very much less if adrenaline left the circulation or was destroyed on its way round He therefore investigated the effect of intra brachial infusions ranging from $\frac{1}{10}$ to $\frac{1}{1000}$ μg /min In all these after the initial transient vaso dilatation the flow was unchanged or very slightly increased There was no sustained vasodilatation in any way comparable to that during 10 μg /min intravenous infusions Both Swan and Duff and Whelan are agreed that the sustained vaso dilatation cannot be due to a direct local action of the adrena line (Whelan s estimate that not more than $\frac{1}{10}$ μg adr /min would enter the forearm during a 10 μg /min intravenous infusion was made as follows forearm volume 1000 ml resting blood flow 5 ml /100 ml forearm/min Therefore for whole forearm 50 ml /min cardiac output 5 litres There fore fraction reaching forearm is $\frac{1}{100}$ fraction of 10 μg is $\frac{1}{10}$ μg)

Swan and Duff thought that the sustained vasodilatation was mediated by the sympathetic because it was unobtainable in chronically sympathectomized limbs (Fig 3 7 and Table III) However Whelan observed it in the nerve blocked forearm His results are shown in Figs 3 8 and 3 9 Returning to the sympathectomized limb he showed that the sustained vaso dilatation was present a few hours after operation but that it grew less as hours passed between operation and the time of testing (changes in other vascular responses following sympa thectomy are described in Chapter 7) This explained why Duff and Swan had not been able to find it The results of Whelan s experiments on one of his three sympathectomized subjects are shown in Figs 3 10 It appears then that the sustained vasodilatation is definitely not mediated by the sympathetic

The only other explanation left for it is that it is due to the direct action on the muscle blood vessels of some humoral sub stance other than adrenaline This substance might be formed

from adrenaline itself during its passage from the venous to the arterial side or it might be released by adrenaline in some other part of the body Staub (1946) found that intravenous infusion of adrenaline released histamine but Mongar and Whelan (1952) have not been able to confirm this The sus

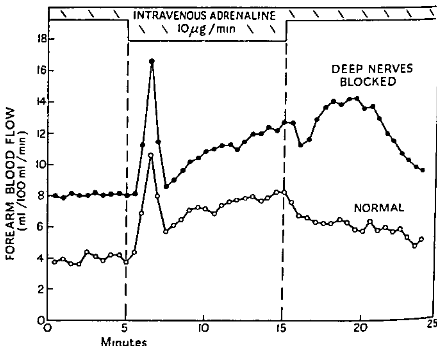


Fig 3 8 Results of experiments on the sustained vasodilatation in muscle caused by intravenous adrenaline

Owing to the release of vasoconstrictor tone resting blood flow in the nerve blocked forearm is about doubled Apart from the difference in the general levels the behaviour of the blood flows during the adrenaline infusion looked very much alike For better comparison the blood flows have been graphed in Fig 3 9 after subtraction of the respective resting rates

Averaged results of 10 infusions on 6 subjects Plethysmograph water temperature 34 3 C (Whelan 1952)

tained vasodilatation is not likely to be due to the release of histamine At present the nature of this substance remains unknown

Before leaving the subject of adrenaline and the blood flow in human muscles mention must be made of a curious response which Whelan (1952) described and which is seen when the sympathetic supply is blocked or severed After stopping an

intravenous adrenaline infusion the blood flow instead of gradually subsiding to the resting level subsides for a short time and then shows a well marked secondary increase This is seen in the nerve blocked forearm in Figs 3 8 and 3 9 in the acutely sympathectomized forearm in Fig 3 10 though not 7 hours after operation in this subject and in the chronically sympathectomized calf in Fig 3 7 It was recorded in a forearm which had been completely denervated by avulsion

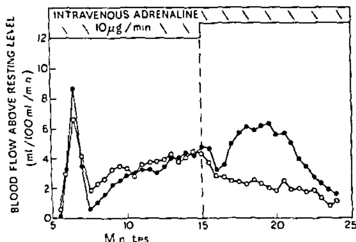


Fig 3 9 Experiment on the sustained vasodilatation in muscle caused by intravenous adrenaline

Results seen in Fig 3 8 graphed after subtraction of the respective resting blood flow

Transient vasodilatation was followed by sustained vasodilatation in both normal and nerve blocked forearms

The sustained vasodilatation cannot be mediated by the sympathetic nerve supply to the skeletal muscle vessels (Whelan 19)

of the brachial plexus (Whelan 19,2) Its significance is not yet known

Finally it is of interest to compare the action of adrenaline on human muscle vessels with its action on those of the cat In the animal muscle blood flow can be recorded by more direct and satisfying methods In studies of muscle blood flow in the intact cat however adrenaline has usually been given by intravenous injection The observed blood flow changes have therefore been limited to those which correspond in time to the transient vasodilatation in man

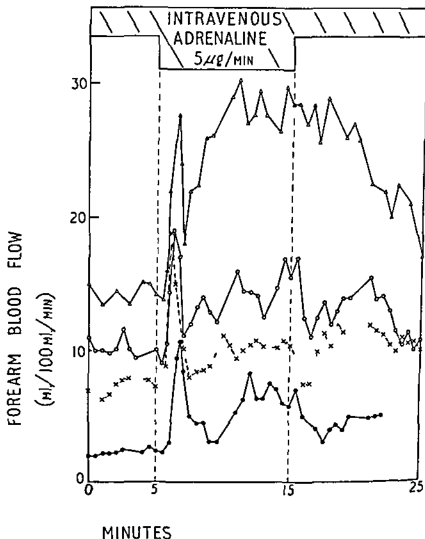


Fig. 3.10. Experiments on the sustained vasodilatation caused by intravenous adrenaline.

Results showing the effect of intravenous adrenaline on the forearm blood flow 2 days before (dots) and 7 hours (triangles), 24 hours (circles) and 4 days (crosses) after sympathectomy.

Transient and sustained vasodilatation are conspicuous in the acutely sympathectomized limb (triangles).

The sustained vasodilatation cannot be mediated by the sympathetic nerve supply to the muscle vessel.

After sympathectomy as hours pass the sustained vasodilatation dwindles. It is absent in chronically sympathectomized limbs (Fig. 3.7). (Whelan 195[illegible])

In this respect there is good agreement between the findings in the two species Hoskins Gunning and Berry (1916) and Gruber (1929) found that small intravenous doses of adrenaline caused active vasodilatation in feline muscle and Clark (1933) and Folkow Frost and Uvnas (1948) showed by intra arterial injection that this was by virtue of its direct action on the muscle vessels

REFERENCES

Abramson D I and Ferris E B (1940) *Amer Heart J* **19** 541

Allen W J (1946) M D Thesis Queen s University Belfast

Allen W J Barcroft H and Edholm O G (1946) *J Physiol* **105** 255

Clark C A (1933) *J Physiol* **80** 429

Dale H H and Richards A N (1918) *J Physiol* **52** 110

Duff R S and Swan H J C (1951) *J Physiol* **114** 41

Folkow B Frost J and Uvnas B (1948) *Acta physiol Scand* **15** 412

Grant R T and Pearson R S B (1938) *Clin Sci* **3** 119

Gruber C M (1929) *Amer J Physiol* **89** 650

Hartman F A Evans J I and Walker H G (1928) *Amer J Physiol* **85** 91

Holling H E (1939) *Clin Sci* **4** 103

Hoskins R G Gunning R E I and Berry E L (1916) *Amer J Physiol* **41** 513

Mongar J L and Whelan R F (195-) *J Physiol In the press*

Staub H (1946) *Schweiz med Wschr* **76** 818

Stead E A (1950) Personal communication

Swan H J C (1951) Unpublished observations

Whelan R F (195) *J Physiol In the press*

Zweifach B W (1949) *Factors Regulating Blood Pressure* Josiah Macy Foundation Caldwell N J Progress Associates

CHAPTER 4

THE ACTION OF NORADRENALINE ON THE CIRCULATION IN SKELETAL MUSCLE

In 1910 Barger and Dale observed that the substance we now call noradrenaline caused responses more like those of sympathetic nerve stimulation than did adrenaline The suggestion by Bacq (1934) that noradrenaline might in fact be the mediator of excitatory sympathetic nerve impulses was not finally accepted until 1946 when von Euler identified it in extracts of organs and nerves His discovery was the starting point of numerous investigations on its action in different organs In this chapter we shall be concerned with its effect on the circulation in human muscle which as we shall see differs from that of adrenaline

The first observations in man on the effect of noradrenaline on the blood flow in muscle were communicated to the Annual Meeting of the American Physiological Society at Detroit in 1949 by Duncanson Stewart and Edholm An abstract of their paper appeared in the *Federation Proceedings* of the same year They found that intravenous infusions caused a slight decrease in forearm blood flow Their finding was later confirmed both in the forearm and calf (Swan 1949 Barcroft and Konzett 1949a b de Largy Greenfield McCorry and Whelan 1950 Barnett Blacket Depoorter Sanderson and Wilson 1950) Fig 4 1 is from the paper by the last named authors Although Barcroft and Konzett did not observe any initial transient vasodilatation during intravenous infusions at 10 μg /min a small one often occurs at the beginning of 20 μg / min infusions after which the blood flow in the forearm returns to about the resting rate (Whelan and Young 1952)

Owing to the presence of both skin and muscle in the plethysmograph and to the fact that noradrenaline constricts cutaneous vessels as is evidenced by pallor of the skin it is difficult to tell with assurance from the experiments just described whether on the average it caused any change in the calibre of the muscle vessels

Barcroft and Konzett (1949) and Swan (1951) investigated the direct action of noradrenaline on the circulation in the calf Fig 4 2 shows at the top the results of short intra arterial infusions In all cases L noradrenaline caused a simple decrease in the calf blood flow in some the flow was reduced by 75 per cent Since skin forms only a small proportion of

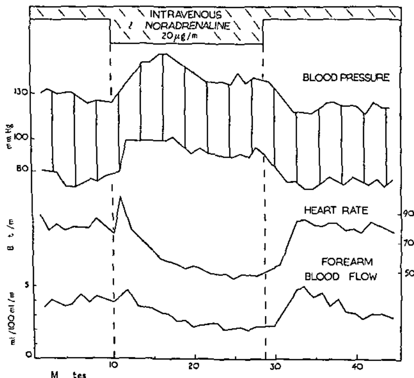


Fig 4 1 Results showing the action of an intravenous infusion of noradrenaline on the forearm blood flow (Barnett Blacket Depoorter Sanderson and Wilson 1950)

the calf they thought it reasonable to conclude that it must have had a direct constrictor action on the muscle vessels

We must now briefly compare the actions of adrenaline and noradrenaline The most striking difference is the absence of the transient vasodilatation in the calf during intra arterial infusions of noradrenaline Fig 4 2 shows clearly that the transient vasodilatation only occurs with adrenaline Barcroft

and Konzett (1949b) found that the transient vasodilatation also occurred with isopropyl noradrenaline which has two methyl groups

It is of some interest too to compare the actions of the two substances from the point of view of deciding which of

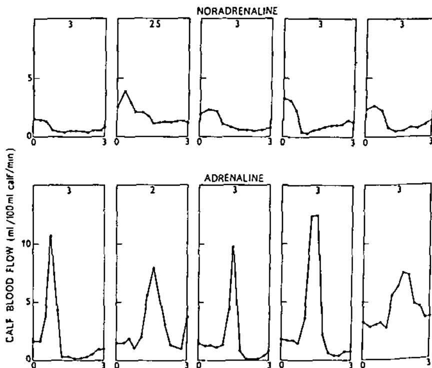


Fig 4 Results showing the action of intra arterial noradrenaline on the circulation in human muscle

Absence of the transient vasodilatation during intra arterial noradrenaline Since the skin forms only a small proportion of the calf and noradrenaline reduced the calf blood flow by as much as 75 per cent it is reasonable to suppose that it had a direct vasoconstrictor action on the muscle blood vessels

The figure under the top margin of each diagram is the rate of infusion into the femoral artery in µg /min Air filled plethysmograph (Barcroft and Konzett 1949)

them is likely to be the transmitter at the sympathetic vaso constrictor nerve endings The following points are relevant

1 Noradrenaline causes simple vasoconstriction This action is manifest during intrafemoral arterial infusions at as low a rate as 0 5 µg per minute (Swan 1951)

2 The local action of adrenaline depends upon the rate of infusion In the calf rates of 1 μg per minute cause transient vasodilatation with a return of the blood flow to approximately the initial level Only when the adrenaline enters the femoral artery at a greater rate does constriction take place (see Chapter 3 Table III)

On the by no means certain supposition that the effects of intra arterial infusions are comparable with those of continuous liberation at nerve endings we can speculate on the probable transmitter substance If it were adrenaline a vasodilatation would have to precede any vasoconstriction also considerable amounts of adrenaline would have to be liberated to cause vaso constriction This would not seem to be the most economical way to cause constriction In contrast noradrenaline in very small doses causes constriction without any vasodilatation and it appears very much more likely that this substance is the mediator of the sympathetic nerve impulses to the muscle vessels

Now let us consider the effect of a circulating mediator in distinction to that liberated at the nerve endings It is un likely that in natural conditions the circulation would contain only adrenaline or only noradrenaline a mixture of very small amounts of both would be expected The question of which of them in a mixture will have the predominant action was one which interested de Largy Greenfield McCorry and Whelan (1950) They recorded the blood flow in six subjects during intravenous infusions of mixtures at the rate of 8–10 μg per minute lasting for 5 minutes Fig 4 3 shows the averaged results Beginning at the top on the left the noradrenaline contents of the mixtures in the six groups of experiments were 18 33 53 75 89 and 100 per cent The figure shows that the effect of adrenaline predominated in mixtures containing as much as 75 per cent noradrenaline This indicates that it is likely that noradrenaline predominates overwhelmingly at the nerve endings

In conclusion there appears to be a difference in the action of intravenous noradrenaline in man and the cat We have seen that in man intravenous infusions usually cause vaso constriction in the forearm and calf (Fig 4 1) however intra venous injections cause vasodilatation in the cat s leg The

observations on the cat were carefully made by Meier, Gross and Eichenberger (1949) and by Cobbold and Vass (1952). Cobbold and Vass have shown that this vasodilatation is in the vessels supplying leg muscles and that it is only transient; for in intravenous infusions it soon gives place to sustained constriction. The initial vasodilatation appears to be due to the

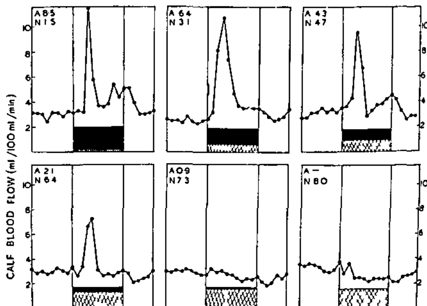


Fig. 4.3. Results showing the effect on the calf blood flow of intravenous infusions of adrenaline-noradrenaline mixture containing 18, 33, 57, 7 . 89 and 100 per cent. noradrenaline respectively.
The transient vasodilator action of adrenaline was . . . till the proportion of noradrenaline was more than . . . per cent.
Averaged result of six experiments . . . min. infusion. Black rectangle, adrenaline. Hatched rectangle, noradrenaline. (de Largy, . . . McCorry and Whelan, 19 0.)

abrupt rise in blood pressure and the subsequent constriction to the more gradual development of the constrictor action of noradrenaline on the muscle vessels. The prevention of the rise in blood pressure by a compensator abolishes the initial vasodilatation and only the subsequent constriction is seen.

In the cat, as in man, in all effective intra-arterial doses it has a direct vasoconstrictor action upon the muscle vessels (Cross, 1949; Folkow, Frost and Uvnas, 1948).

REFERENCES

Bacq Z M (1934) *Ann Physiol Physicochim biol* **10** 467
Barcroft H and Konzett H (1949a) *Helv physiol pharmacol Acta* **7** C4
—— (1949b) *J Physiol* **110** 194
Barger G and Dale H H (1910) *J Physiol* **41** 19
Burnett A J Blacket R B Depoorter A E Sanderson P H and Wilson G M (1950) *Clin Sci* **9** 151
Cobbold A F and Vass C C N (1952) *J Physiol In the press*
Duncanson D Stewart T and Edholm O G (1949) *Fed Proc* **8** 37
Euler U S von (1946) *Acta physiol scand* **12** 73
Folkow B Frost J and Uvnäs B (1948) *Acta physiol scand* **15** 412
Gross F (1949) *Helv physiol pharmacol Acta* **7** C 43
Largy C de Greenfield A D M McCorry R L and Whelan R F (1950) *Clin Sci* **9** 71
Meier R Gross F and Eichenberger E (1949) *Helv physiol pharmacol Acta* **7** 230
Swan H J C (1949) *Lancet* **2** 508
—— (1951) Unpublished observations
Whelan R J and Young I M (1952) *Brit J Pharmacol In the press*

CHAPTER 5

THE CIRCULATION IN SKELETAL MUSCLE DURING EXERCISE

It is generally believed that sympathetic nerves and hormones perform important functions during stress. Their action upon the circulation in active muscle is therefore of special interest. But before discussing this it will be convenient to describe some experiments on the effect of exercise on muscle blood flow. These can be divided into two groups—those on the effect of sustained and those on the effect of rhythmic contraction.

Sustained Contraction

In 1877(a, b) Gaskell established by experiments on the dog and frog that the two most important vascular changes taking place in skeletal muscle during sustained contraction are vasodilatation and opposed to this mechanical compression. Later the relative importance of the vasodilatation and of the compression became the subject of an interesting controversy between Anrep's and Rein's laboratories.

In man the existence of these factors had been recognized (Lindhard, 1920a, b) but there was some difference of opinion as to their significance. Dolgin and Lehmann (1930) compared the times for which graded strengths of hand grip could be *maintained with and without previous circulatory arrest in the* upper arm. The duration of the weak grips was shortened by the arrest, but that of the strong ones was not affected. They concluded that in strong grips the circulation had been arrested in the muscles. Yandell Henderson and his colleagues (1936) studied the effect of contraction of the calf muscles on the intramuscular pressure as recorded by a needle and water manometer. As strong contractions only caused a very small rise in intramuscular pressure they concluded that there could not be much resistance to the blood flow. Grant (1938) used the plethysmograph to record the changes in forearm blood flow during strong hand grips. He found a slight rise in flow during the contraction and a large one immediately after. He con

cluded that vasodilatation occurred during sustained contraction but was restricted

Barcroft and Millen (1939) also studied the behaviour of the blood flow during sustained contraction The principle of their method was as follows Muscle temperature was recorded thermoelectrically By immersing a limb in hot or cold water for an hour or more a constant difference in temperature could be achieved between a muscle and the blood entering it (at approximately body temperature) Sustained contraction was then performed Hyperaemia could be inferred if hot muscle cooled and if cold muscle became warmer and if these temperature changes were abolished by previous circulatory arrest

The muscles used were those in the calf of the leg Details of the self retaining thermojunction and of its insertion into the calf muscles will be found in the original paper Four different strengths of contraction were studied namely 0 05 0 1 0 2 and 0 3 maximal (According to Weber (1846) Koster (1868) Hermann (1898) and Peys (1915) the limiting load on the ball of the foot is about 225 kg and the pull on the Achilles tendon about 675 kg —more than half a ton) To perform any one of the three weaker contractions the subject sat with one leg in a waterbath (a dustbin) and keeping his knee straight exerted a steady pressure with the ball of the foot on a stirrup attached to a suitably weighted lever To perform the strongest the 0 3 maximal he stood on tiptoe with the knee straight on the leg in the waterbath The two strongest contractions and all the contractions performed during previous circulatory arrest in the thigh were maintained till discomfort became intolerable The two weaker ones were given up after a quarter and half an hour respectively and no acute discomfort was felt

The results obtained in the weakest contraction are shown in Fig 5 1 The upper curve on the left hand side shows that the temperature of the warmed muscle fell during exercise the curve immediately below it shows that the temperature of the cooled muscle rose It tended to approach the temperature of the blood entering it This suggested hyperaemia The results obtained when the exercises were performed during circulatory arrest are shown on the right hand side They were quite different there was a slight rise in the temperature of

both the warmed and the cooled muscle which could have been due to metabolic heat production The convergence of the temperature towards body temperature observed when the circulation was free was not seen and must have been due to hyperaemia

In this experiment the exercise performed with free circulation lasted half an hour and could have been kept up for longer

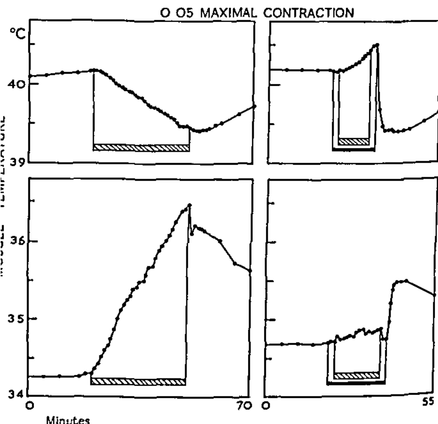


Fig 1 Result showing that weak sustain l contracti n of the human ga trocnemiu sole i mu le is a ompanied by hyp ra mia

Upper curve Waterbath t mperature 4 C l t m sel

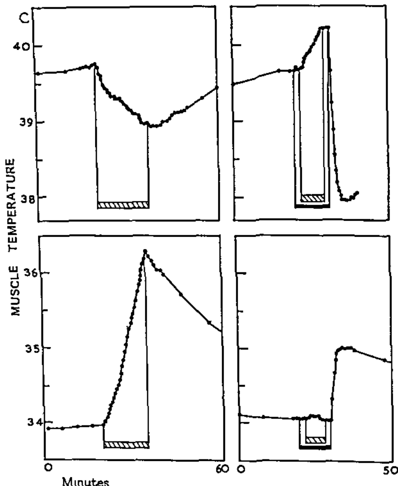
Lower curve Waterb ath temp rature 3 C ll m sel

Hatched recta gl 0 maximal tr ti n

Sol l rectangle l t a rested i th thigh

Left During ex so the t perat re f th m l appr l l ll l temperature The c ul l hav l en l t t hyperaemia

Right Confirmed by abse ce f these t mperature ch nges l ri g ex rcise performed with arrested circulation



F g 5   Re ults show ng that weak su tain d cont action of the l uman ga trocn mius sol us m is le s accompanied by hyperaem a

Upper cu ve   Waterbath tempe ature 4 C   hot mu cle
Lou   urve   Wate bath temperature 3? C   cold mus l
Hatch d rectangle 0 max mal contraction
Sol l rectangl   ulat on arre t d in th th gh
L ft D i g ex cise the temperature of th muscle approa h l blood t mpe atu e Th coul l have been due to hyperaem a
R ght Confirm l by absen e of the t mperature chang s dur ng exerci e pe form l w th arre t d re lati n

When done with the circulation arrested however it had to be stopped after about 10 minutes because of unendurable discomfort The absence of fatigue in the free circulation experiment was consistent with the conclusion that the muscle was receiving an adequate supply of blood

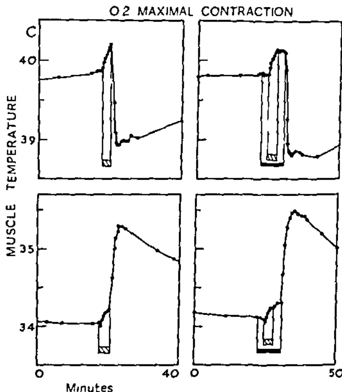


Fig 5 3 Result showing that strong sustained contraction of the gastrocnemius soleus muscle is ischaemic
Upper curve Waterbath temperature 4- C hot muscle
Lower curve Waterbath temperature 3 C cold muscle
Hatched rectangle 0 5 maximal contraction
Solid rectangle circulation arrested in the thigh
During exercise the temperature of both hot and cold muscl increased when circulation free and when it was arrested There could not have been any appreciable blood flow through the muscle in either case

Hyperaemia also of functional significance occurred too during the 0 1 maximal contractions as will be seen from Fig 5 2

The behaviour of the circulation during the stronger contractions was altogether different Fig 5 3 shows the results

of the 0 2 maximal one During contraction the temperature of both hot and cold muscle increased In the absence of any sign of approximation of the temperature of the hot muscle to that of the blood it was difficult to believe that there could have been hyperaemia Indeed the striking similarity between the temperature changes recorded while the circulation was free and those obtained during circulatory arrest strongly suggested that there could have been no circulation in either case This could easily be explained on the grounds that the intramuscular tension had overcome the arterial blood pressure and occluded the vessels supplying the muscle Moreover the duration of the exercise performed with free circulation and maintained for as long as possible was no longer than that in the corresponding circulatory arrest experiment Such a result would be expected if there was no circulation through the muscle in either case

The temperature changes after relaxation are also instructive Fig 5 3 shows that the temperatures of the hot and of the cold muscle changed abruptly in the direction of that of the blood This and the delay of similar temperature changes in the circulatory arrest experiment till after the circulation had been released signifies that they were caused by marked hyperaemia Marked hyperaemia would be expected after release of the circulation to potentially widely dilated vessels

The results of the strongest contraction the 0 3 maximal tiptoe standing on one leg shown in Fig 5 4 were similar as also was the inference that mechanical compression had arrested the circulation through potentially dilated muscle vessels

A number of interesting points need discussion Perhaps the most striking finding is the suddenness of the change from hyperaemia to ischaemia with increasing strength of contraction After relaxation of the 0 1 maximal contraction the blood flow apparently began to subside almost at once there was no evidence of the removal of any mechanical obstruction Yet a 10 per cent increase in the strength of contraction changed the whole picture to one of ischaemia On the one hand the exercise was given up voluntarily after a quarter of an hour and on the other it became intolerable in less than 5 minutes It seems that the circulation through the calf muscle must have been very free below a critical strength of

contraction (between 0 1 and 0 2 maximal) and nearly or quite obstructed above the critical point

Marschak (1931) found that strenuous contraction of the forearm muscles could obliterate the radial pulse This suggests that ischaemia of the calf muscles could conceivably have been due to nipping of the main artery or vein This would reconcile Henderson s (1936) finding of low intramuscular

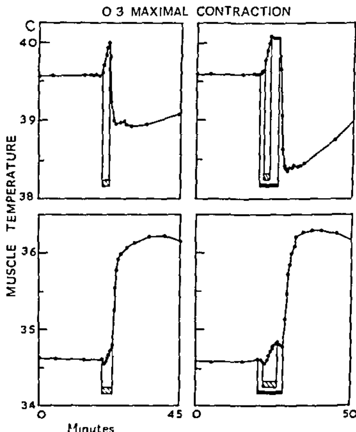


Fig 5 4 Results showing that strong sustained contraction of the gastrocnemius soleus muscle is ischaemic
Upper curve Waterbath temperature 4[illegible] C [illegible] muscle
Lower curve Water bath temperature 3[illegible] C [illegible] muscle
Hatched rectangle [illegible] maximal contraction
[illegible] rectangle circulation arrested [illegible] thigh
During exercise the temperature of both [illegible] and [illegible] muscle increased when circulation free and when it was arrested There could not have been any appreciable blood flow through the muscle in either case

pressure with our finding of ischaemia It would be interesting to repeat his experiment

It will be remembered that Grant (1938) concluded that strong sustained contraction of the forearm muscles did not prevent hyperaemia but restricted it This was because there was a slight increase in forearm blood flow during contraction and a large increase after There may have been a small increase in flow not shown by our method during the two strongest contractions Another interpretation of Grant's results seems possible During contraction there may have been ischaemia in most muscles and hyperaemia in a few The hyperaemia might account for the small increase in flow found during the contraction After relaxation the rush of blood through the previously ischaemic muscles could explain the conspicuous increase in flow

It is interesting to recall that Gaskell (1877a) found that the blood flow gradually increased during tetanic stimulation of the dog's extensor muscles Similar results have been obtained for the dog's gastrocnemius even during strong stimulation (Rein Mertens and Schneider 1935 Kramer and Quensel 1937 Bulbring and Burn 1939 The increase was manifest after a minute's contraction But there was no sign of this during our two stronger contractions which lasted still longer This is probably explained by the fact that the dog's muscle may have been contracting weakly even though strongly stimulated The importance of the tension developed in the muscle does not seem to have been appreciated Kramer and Quensel do not mention the strength of their contractions Rein et al apparently tied the Achilles tendon to a 1 kg weight so that the tension developed could not have exceeded that amount Bulbring and Burn recorded tensions of about 18 5 kg but these soon fell to 5 kg Yet the maximum strength of contraction of the cat's gastrocnemius is 12 5 kg (Eccles and Sherrington 1930) and by analogy that of the dog should be about 35 kg The reason why strong stimulation apparently elicited weak contraction in the dog is not clear

The Muscle Pump

Before discussing the behaviour of the blood flow through rhythmically contracting muscle a few words must be said on

the subject of the muscle pump Its action in man has been demonstrated by Smirk (1936) who recorded the pressure in a vein in the dorsum of the foot of a subject standing upright Marked fall in pressure occurred when the subject raised and lowered his heels rhythmically due to emptying of the leg veins by the pumping action of the muscles Further interesting work along these lines has appeared by Pollack Taylor Myers and Wood (1949) and by Walker and Longland (1950)

The action of the muscle pump can very easily be shown with the plethysmograph (Barcroft and Dornhorst 1949a) Fig 5 5 is from an experiment in which calf volume was

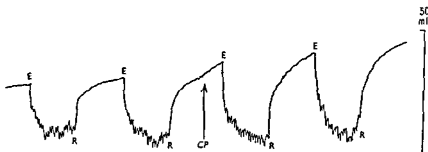


Fig 5 5 Plethysmographic record of the volume of the calf of leg Shrinkage denoted by downward movement of writing point
Results showing shrinkage in calf volume during rhythmic exercise due to the action of the muscle pump
E pedal pressed down once a second for 10 sec *R* rest for 10 sec *CP* cuff just above knee inflated to 90 mm Hg till end of recording (Barcroft and Dornhorst 1948)

recorded with the plethysmograph in a subject lying down Periods of 10 sec of flexion and extension of the foot alternated with periods of 10 sec rest During exercise pressure was exerted about once a second to the sound of a metronome with the ball of the foot on a suitably weighted pedal Calf volume decreased at the beginning of the exercise as the blood in the veins was pumped out (Fig 5 5) Increase took place at the beginning of each rest period as they refilled The muscle pump has considerable power When the venous pressure was raised to 90 mm Hg by inflation of a cuff above the knee the volume of the calf still shrank at the beginning of exercises The contractions had forced the blood out under the cuff

Rhythmic Contraction

The experiments on static contraction suggest that there would be free hyperaemia in muscle during gentle rhythmic contractions During strong ones however an intermittent flow would be expected stasis during contraction and free flow through widely dilated vessels during relaxation This had not been studied plethysmographically in man as it had been assumed that the to and fro movements of the muscles would interfere with recording Thanks to the ingenuity of Dr A C Dornhorst it has now been done Details of the method are given in the original paper (Barcroft and Dornhorst 1949b) and shown in Fig 5 6 Calf volume was recorded with the plethysmograph in the supine subject as in the previous experiment on the muscle pump The subject pressed the pedal once a second to the sound of a metronome relaxing as completely as possible after each contraction After the initial pump out of the venous blood the record usually showed very even up and down movements of the recorder due to the to and fro movement of the calf muscles This may be seen in Fig 5 7 Inflation of the thigh cuff to a pressure of about 90 mm Hg was usually followed by a regular upward trend of the oscillations from which the inflow could easily be estimated However this was only the apparent inflow for some blood was usually forced out under the cuff by the muscle pump To estimate the rate of blood loss the inflow was arrested by digital compression of the femoral artery in the groin There was usually a regular downward trend of the oscillations from which the outflow could easily be estimated (Fig 5 7) This figure was added to the apparent inflow To see whether arterial compression had succeeded in arresting the inflow the subject then stopped exercise Escape of blood from the calf was prevented by the venous occlusion cuff If the inflow had ceased the recorder drew a horizontal straight line In some subjects though there were no pulsations the line sloped gently upwards due to unavoidable inflow from collateral vessels A small allowance was made for this in the calculation

Fig 5 8 shows the blood flow results obtained before during and after six minutes of strong rhythmic exercise The blood



(A)

(B)

Fig 5 6 Apparatus used in the experiments on the blood flow in the calf during rhythmic exercise

The plethysmograph hung and counterpoise weight (A) collecting cuff on the lower part of the thigh ankle cuff for arresting the circulation in the foot heels resting on fixed supports feet on pedals horizontal bars at right angles to pedals each is pivoted separately where pedal and bar join weights on bars for adjusting work done pointer actuated by movement of pedal and bar on right side (B) stops at head end of bar one for taking weight off pedal during relaxation the other to prevent movement of pointer beyond end of scale (A) metronome (B) straps supporting subject's shoulders (A) control lever on end of kymograph table (A) The subject is looking at the pointer (Barcroft and Dornhorst 1949)

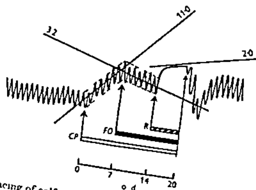


Fig 7 Tracing of calf volume changes during rhythmic exercise showing procedures for determining the ex re e fl w At CP a collecting pressure of 30 mm Hg was applied 7 s later at FO the femoral artery was occluded After a further 7 sec at R the subject relaxed for 6 sec (Barcroft and Dornhorst 1949)

Fig 5 8 Results h w i g the l la i u of the ll l fl w n tl alf lu ng rythm c exe
Black lots m an rate of fl w M l at n reas n l loo l fl w
Crosses ate of fl w lu ng a f w con ls r laxat n Rap l blood flow
Ci l ate of fl w l r ng a f w econ l ıt ta e l ont act on Slightly n ea el l ood fl w
A ng l result S t al j t

flow increased both during the exercise and immediately after This proves that it was obstructed mechanically There is no alternative explanation for the sudden increase in the flow immediately afterwards But the obstruction did not prevent hyperaemia The blood must have been flowing in spurts its progress being obstructed during contraction and free through widely dilated vessels during relaxation Fig 5 8 shows further evidence to the same effect The exercise was interrupted eight

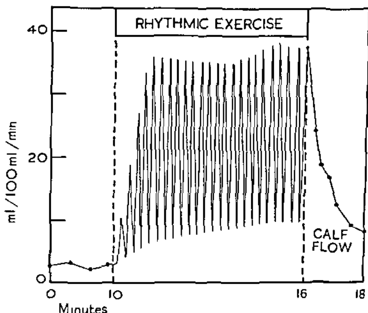


Fig 5 9 Diagrammatic representation of changes in blood flow in the calf during strong rhythmic contraction

times for a few seconds each time four times to record blood flows *during sustained pressure on the pedal and four times* while the subject relaxed the calf muscles as completely as possible The results show as would be expected, restricted flow during sustained contraction (circles) and free flow during relaxation (crosses) This is seen diagrammatically in Fig 5 9

It is interesting to compare the results obtained in our experiments (Fig 5 8) with those obtained on the dog s gastrocnemius by Kramer Obal and Quensel (1937) *and shown in*

Fig 5 10 They are very alike Their interpretation too is the same as ours

The experiments just described show that the circulation in calf muscles during strong rhythmic contraction is affected by three factors local vasodilatation mechanical obstruction and the muscle pump They enable us to visualise the spurting blood flow the overall hyperaemia the forceable return of blood to the heart the shrunken veins and paradoxically the redistribution of blood from the calf to other parts of the vascular system

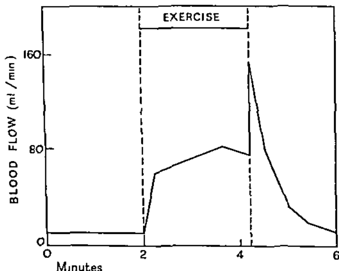


Fig 5 10 Experiment showing the effect of rhythmic exercise on the blood flow through the chloralosed dog s gastrocnemius muscle The changes are strikingly like those recorded in man Fig 5 8 (Kramer Obal and Quensel 1937)

REFERENCES

Barcroft H and Dornhorst A C (1949a) *J Physiol* **108** 39P
—— (1949b) *J Physiol* **109** 402
Barcroft H and Millen J L E (1939) *J Physiol* **97** 17
Bulbring F and Burn J H (1939) *J Physiol* **95** 203
Dolgin P and Lehmann G (1930) *Arbeitsphysiologie* **2** 248
Eccles J C and Sherrington C S (1930) *Proc roy Soc B* **106** 326
Gaskell W H (187 a) *J Anat* **11** 360
—— (187 b) *J Anat* **11** 720
Grant R T (1938) *Clin Sci* **3** 157

Henderson Y A Oughterson A W Greenberg L A and Searle C P (1936) *Amer J Physiol* **114** 261
Hermann L (1898) *Pflug Arch ges Physiol* **73** 429
Koster W (1868) *Ned Arch Genees Natuurkunde* **3** 34
Kramer K Obal F and Quensel W (1937) *Pflug Arch ges Physiol* **239** 620
Lindhard J (1920a) *Skand Arch Physiol* **40** 145
—— (1920b) *Skand Arch Physiol* **40** 196
Marschal M (1931) *Arbeitsphysiologie* **4** 1
Pollack A A Taylor B E Myers T T and Wood E H (1949) *J clin Invest* **28** 559
Rein H Mertens O and Schneider M (1935) *Pflug Arch ges Physiol* **236** 636
Reys J H O (1915) *Pflug Arch ges Physiol* **160** 183
Smirk F H (1936) *Clin Sci* **2** 317
Walker A J and Longland C J (1950) *Clin Sci* **9** 101
Weber E (1846) *Wagner's Handwörterbuch d Physiol* **3** 89

CHAPTER 6

THE ACTION OF SYMPATHETIC NERVES ON THE CIRCULATION IN SKELETAL MUSCLE DURING EXERCISE

In Chapter 1 it was shown that the vasomotor centre maintains vasoconstrictor tone in the blood vessels of skeletal muscle It was natural to wonder whether this was released in exercise and if so to what extent it was responsible for the

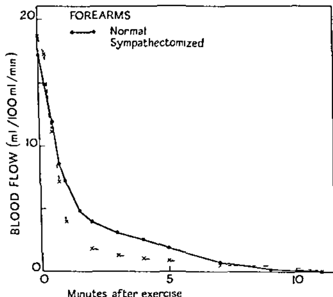


Fig 6 1 Results showing vasodilatation in sympathectomized muscle after exercise Average results of experiments on one subject (Grant 1938)

increase in blood flow through the active muscles It will be remembered that Grant (1938) had found that during exercise the vasodilatation in normal and sympathectomized limbs was similar and concluded that it was due in the main to the action of metabolites This may be seen in Fig 6 1 which has been drawn from his results However athletes find that they run

better if they "warm up" before a race and the explanation of "warming up" might be that the rise in body temperature caused the vasomotor centre to release the constrictor tone in their muscle and so potentiated the vasodilator action of the metabolites

This possibility was investigated by Barcroft Dornhorst

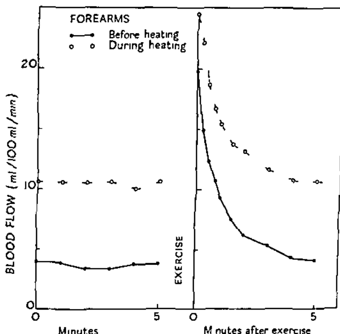


Fig 6 . Results showing the effect of releasing sympathetic vaso constrictor tone in muscle on the resting and post exercise blood flow in the forearm

Apart from an increase in the general level of blood flow the post exercise changes look alike To enable more accurate comparison they have been superimposed and graphed in Fig 6 3

Each subject did 3 rhythmic exercises lasting 3 to 4 minutes before and after release of vasoconstrictor tone Tone released by immersion of feet in water at 45 C Plethysmograph water filled temperature 34–3 C

Averaged result on 4 subjects

McClatchey and Tanner (1951) The general plan of their experiments was as follows If release of constrictor tone speeded up the circulation in working muscles the rate of accumulation of metabolites should be retarded At the end of the exercise the hyperaemia and blood debt should be reduced (Lewis and Grant 1925 Freeman 1935 Kunkel

Stead and Weiss 1939 Abramson Katzenstein and Ferris 1941 Fichna and Wilkins 1941) To see if this was so, carefully standardized rhythmic exercises were performed with the forearm or calf and the resulting hyperaemia and its subsidence were measured with the plethysmograph One or more of the subject's limbs was then immersed in water at 45 C to raise his body temperature and release his constrictor tone (Barcroft Bonnar and Edholm 1947) The exercises were then

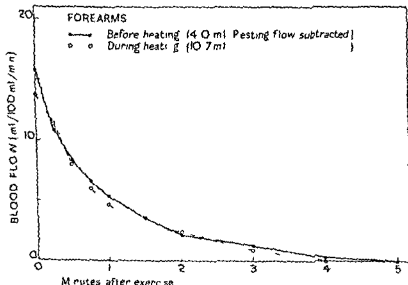


Fig 6 3 Post exercise blood flow changes recorded in the forearm muscles before and during release of sympathetic vaso constrictor tone Fig 6 2 Graphed after subtraction of the respective post exercise resting rates The difference in the blood debts (areas under the curves) is only 9 7 per cent (Barcroft Dornhorst McClatchey and Tanner 1952)

repeated and the ensuing vascular changes recorded and compared with those previously obtained

Fig 6 2 shows the results The resting blood flow was 4 0 ml per 100 ml forearm per minute after the release of tone it rose to 10 7 ml Apart from the increase in the general level of the circulation the post exercise changes looked rather alike To compare them more accurately the respective resting rate was subtracted from the post exercise rate in each case and they were graphed as shown in Fig 6 3 The difference

in the blood debts (areas under the curves) was only 9 7 per cent Further experiments on the calf were done on a much larger number of subjects Fig 6 4 shows the results of the first series superimposed after subtraction of the respective resting rates There was no difference Fig 6 5

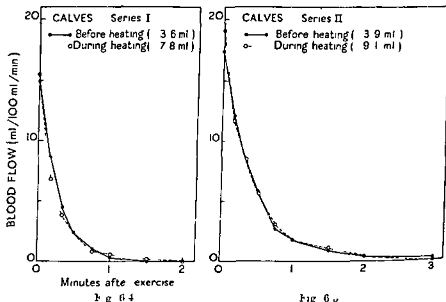


Fig 6 4 Fig 6 5

Figs 6 4 6 5 Post exercise calf blood flows recorded before and during release of sympathetic vasoconstrictor tone in the calf muscle Graphed after subtraction of the respective post exercise resting rates

Releasing vasoconstrictor tone scarcely affected the circulatory changes after exercise

Fig 6 4 Averaged results of experiments on 14 subjects Each did ¼ ½ ¾ 1 and 2 min rhythmic exercise before and during reflex vasodilatation

Fig 6 5 Average results of experiments on 9 subjects Each did 1 4 and 8 min rhythmic exercise before and during reflex vasodilatation (Barcroft Dornhorst McClatchey and Tanner 1952)

shows the results of a second series the post exercise changes were the same

Considering all these results on the forearm and calf there was no reasonable escape from the conclusion that the activity of the vasomotor centre had had no effect on the circulatory changes taking place during or after muscular activity In deed it could hardly have been acting on the same vessels as the metabolites If so surely there would have been some

inverse relation between the general level of the blood flow and the blood debt

To sum up then release of sympathetic vasoconstrictor tone increases the blood flow through muscle (Chapter 1) but apparently not through the same vessels as subserve its metabolic requirements What is the anatomical basis of this? The facts would be simply explained if the vascular bed contained arterio venous anastomoses if the vasomotor centre regulated them in the general interests of the circulation and if the capillary bed was controlled by metabolites according to local requirements But the classical descriptions of muscle vessels by Spalteholtz (1888) and Krogh (1922) do not include A V anastomoses Yet recent observations on living tissues by Zweifach (1949) have convinced him that minute anastomoses or preferential channels exist in many tissues including skeletal muscles where their presence was hitherto unsuspected It is very important to see if this can be confirmed If so our understanding of the circulation in muscle would be considerably extended

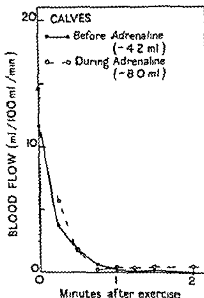


Fig 6 6 Results showing that increasing resting muscle blood flow by intravenous infusion of adrenaline scarcely affected the circulatory changes in the calf following exercise Each subject did 2 or 3 rhythmic exercises lasting ½ min before and during the infusion Averaged results experiments 6 subjects

It will be recalled that intravenous infusions of adrenaline caused a sustained increase in the blood flow in muscle due it was thought to the action of an unknown circulating hormone (Chapter 3) Experiments were therefore done to see if the release of vasoconstrictor tone by adrenaline would

increase the rate of repayment of the blood debt (Swan and Swan 1951) During the exercises the blood flow was probably relatively small as the muscles were never relaxed completely Fig 6 6 shows the results Adrenaline increased the average resting blood flow in the calf from 4 2 to 8 0 ml per 100 ml per minute The average post exercise blood flows obtained after subtracting the respective resting rates were again similar Although the similarity is not quite so perfect as that obtained by Barcroft et al it is clear that the difference in post exercise repayment is slight It is worth mentioning that the adrenaline made the exercise more difficult fatigue did not occur to any greater extent but muscular tremor and incoordination of fine movements impeded the rhythm of action It appears then that increasing the rate of the circulation in the muscle by adrenaline does not hasten the repayment of the blood debt and this too suggests that the vessels controlled by the sympathetic may be different from those controlled by the metabolites

The existence of two circulations in muscle—nutritive and anastomotic—may explain an important discrepancy between the results of plethysmographic and sodium clearance experiments The radio active sodium method introduced by Kety (1949) is briefly as follows Sodium 24 is injected into a muscle and is cleared from it at a rate depending on the ability of the local circulation to remove it To determine the clearance counts are made over the muscle with a Geiger Muller counter and plotted semi logarithmically against time A downward sloping line results whose steepness depends upon the rate of the nutritive blood flow and is denoted by a constant k Using this method to study circulation in the gastrocnemius McGirr (1952a b) found that the rate of clearance from the muscle was decreased during reflex heating Rapaport Saul Hyman and Morton (1952) observed that the clearance from the calf muscles was not increased by lumbar sympathetic block These differences from the results of the plethysmographic method (Chapter 1) would be explained if the vessels controlled by the sympathetic in muscle were arteriovenous anastomoses Increase in blood flow through anastomotic vessels due to reflex heating or lumbar block would not be detected by the sodium clearance method However the

difference between the results of the two methods may well be due to some other cause and further work is needed to explain it

REFERENCES

Abramson D I Katzenstein K H and Ferri F B (1941) *Amer Heart J* **22** 329
Barcroft H Bonnar W McK and Edholm O G (1947) *J Physiol* **106** 271
Barcroft H Dornhorst A C McClatchey H M and Tanner J M (1951) *J Physiol* **117** 391
Fichna L W and Wilkins R W (1941) *Bull Johns Hopk Hosp* **68** 450
Freeman N F (1935) *Amer J Physiol* **113** 384
Grant R T (1938) *Clin Sci* **3** 157
Kety S S (1949) *Amer Heart J* **38** 321
Krogh A (1922) *The Anatomy and Physiology of the Capillaries* New Haven Yale University Press
Kunkel P Stead E A and Weiss S (1939) *J clin Invest* **18** 225
Lewis T and Grant R T (1925) *Heart* **12** 73
McGirr E M (1952a) *Brit med Bull* **8** 192
—— (1952b) *Clin Sci* **11** 91
Rapaport S I Saul A Hyman A and Morton M F (1952) *Circulation* **5** 595
Spalteholtz W (1888) *Abh d sachs Ges d Wiss Math Physik Kl* **14** 509
Swan H J C and Swan D N (1951) Unpublished observations
Zweifach B W (1949) *Factors Regulating Blood Pressure* Josiah Macy Foundation Caldwell N J Progress Associates

CHAPTER 7

SYMPATHETIC DENERVATION

Changes in the behaviour of sympathectomized blood vessels can conveniently be divided into two categories—early and late The early changes have to do with the development of intrinsic tone and the later ones concern the re establishment of connection with the vasomotor centre It will be convenient to describe these separately

THE EARLY CHANGES

Goltz and Freusberg (1874) seem to have been the first to notice that the vasodilatation following denervation only lasts a short time They found that a freshly denervated dog s leg was warmer than its fellow but that the difference did not persist other observers have confirmed the phenomenon in animals (McDowall 1938)

In man the early results appeared to conflict Adson and Brown (1929) found that lumbar sympathectomy caused a permanent rise in the temperature of the toes of 12° C On the other hand Lewis and Landis (1929) deduced from inspection of the skin that the capillary vessels recovered their tone two days after operation and from palpation of the digital arteries that the arteries had contracted considerably by the fourth day More recently a number of observers have shown with the plethysmograph that there is very little difference in the blood flow before and some weeks or months after sympathectomy (Grayson 1948 Grant and Pearson 1938 Wilkins and Eichna 1941)

To obtain more quantitative data on the circulatory changes in human vessels following sympathectomy the blood flow in the hand and foot was measured daily with the plethysmograph before and for some time after nerve section For use in the wards the technique was simplified air filled perspex plethysmographs were used and the recording apparatus was mounted on a trolley cupboard Fig 7 1 shows the apparatus being used to determine the blood flow in the foot Further

details of the method will be found in the original articles (Barcroft and Walker 1949 Lynn and Barcroft 1950 Walker Lynn and Barcroft 1950) Only the results obtained on limbs operated upon for excessive sweating or deep venous thrombosis will be described here as they alone represent the response or normal human arterial vessels to sympathetic denervation In the case of all of the feet and some of the hands the preganglionic fibres were severed in the case of the other hands

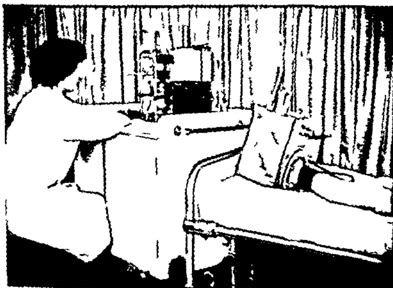


Fig 7 1 Simple plethysmographic apparatus for use in the ward (Photographed by E V Willmott Postgraduate Medical School of London University)

the section was predominantly though not entirely through the postganglionic fibres

Table IV and Fig 7 2 (left) show the effect of sympathectomy on the circulation in the hands After disconnection of the vessels from the vasomotor centre and the release of vasoconstrictor tone there was an immediate eight fold increase in the blood flow This hyperaemia subsided quickly on the sixth day the blood flow was only double the initial rate and on the fourteenth the difference was still less The figure shows that the fingers remained warm though unfortunately the temperature records are incomplete

TABLE IV

o	S x	Age	Rt or Lt	Blood flow (ml per 100 ml hand or foot): B f re l tion, t y	B f re l tion, 1 y	Op	After op at on, 1 d y	1 y	3 days	4 lays	5 days	6 lays	14 day	1 3 m	D g t l temperature: B f operation, 2 days	B f operation, 1 d y	After op rat on, 1 day	6 7 days	14 days	1–3 mos
HANDS																				
	F	35	Rt	3 4	9	18 4	38 0	10 7	11	6 7	9 2	6 8	5 9	—	—	—	34 9	3	3	—
			Lt	5	6	1 5	7	10 6	10 9	8	7 6	6 8	4 5	—	—	—	35 0	3 6	3 1	—
	M	39	Rt	0	0 7	45 6	53 4	34	16 2	30 0	1? 7	16 0	6 8	—	—	? 3	34 7	29 5	34 3	—
			Lt	4 3	8 9	59 ?	48 3	7 7	9	19	0 4	0 7	11 8	—	—	3 6	3 4	3 3	—	—
	M	46	Lt	3	0 9	54 6	30 5	9 9	?	8 4	2 1	18 1	11 5	—	—	—	—	—	—	—
	A rage			**6 7**	**5 2**	**39 1**	**38 6**	**22 7**	**16 7**	**18 5**	**14 4**	**13 7**	**8 1**	—	—	—	**34 3**	**31 7**	**33 0**	
FEET																				
	F	19	Rt	1	1 0	18 0	1 0	0 0	1 0	7 0	6 8	7 6	—	6 6	5 6	4 5	30 4	3? 0	—	33 0
			Lt	0	1 5	15 0	16 0	1 4	11 0	7 0	7 8	9 0	—	5 5	?5 3	6 0	30 0	3? 3	—	31 7
	F	13	Rt	1 3	3	—	18 3	0 8	16 6	9 2	12 ?	9 0	—	6 6	24 0	3 5	33 3	31 0	—	31 5
			Lt	4		—	14 1	1	15 0	9 4	13 4	8 0	—	6 0	?4 0	3	3 0	31 5	—	3 0
	F	40	Lt	4 0	4 0	—	12 8	14 5	0	16 0	13 0	13 0	—	8	—	29 5	35 0	33 5	—	3 0
	F	34	Lt	1 6	1 7	—	8 0	0	14 5	14 6	10 6	4 4	—	1 9	2 0	3	35 4	33 7	—	3 3
	A g			**2 1**	**2 1**	**16 5**	**18 4**	**20 0**	**14 9**	**10 5**	**10 6**	**8 5**	—	**4 9**	**24 2**	**25 0**	**32 7**	**32 3**	—	**32 1**

A test w re n t d o these d th figures used w those l t ned w thin o o two d ys

The results obtained on the feet are also shown in Table IV and in Fig 7 2 In general they resemble those obtained on the hands The maximum flow did not occur till two days after the sympathectomy and was only about half that in the hands The final flow 2–3 months later was about double the preoperative one A large number of toe temperatures were obtained the toes were much warmer after division of their sympathetic nerves and they remained so for 2–3 months

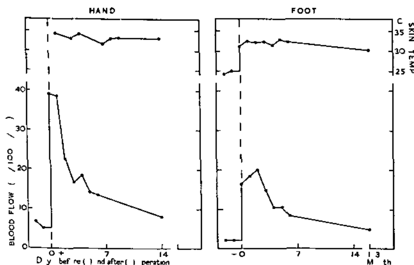


Fig 7 – Results showing the effect of sympathectomy on the blood flow in the hand and foot and on the temperature of the digital skin
The blood flow subsided The digits remained warm
Averaged results from Table I (Walker Lynn and Barcroft 1950)

A number of points need comment It was surprising that the blood flow did not always rise to a maximum at once In three of the five hands the maximum was not reached till the day after the operation Unfortunately the blood flows in four of the feet were not recorded on the day of the operation but in the other two the maximums were recorded on the day after operation in one case and on the second day after in the other This cannot at present be explained

The finding that the maximum blood flow in the hand was about double that in the foot (Fig 7 2) which accords with the observations of Greenfield et al (1951) using a different method

is probably because the circulation in these parts is mainly through the skin and the hand contains a relatively much larger proportion of skin

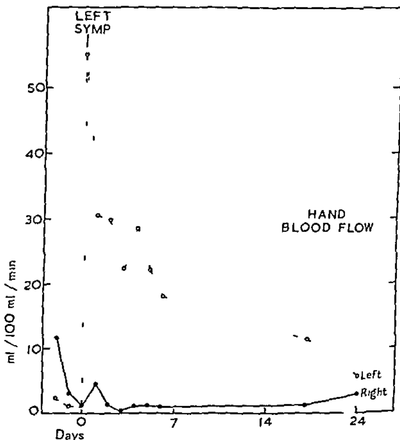


Fig 7 3 Results showing the effect of unilateral sympathectomy on the circulation in the hands
Marked hyperaemia in the ipsilateral hand No change in the circulation in the contralateral hand
The vasodilatation in the ipsilateral hand cannot be due to any factor connected with the operation other than section of the sympathetic fibre (Walker Lynn and Barcroft 1950)

In several cases of which Fig 7 3 is one example the sympathetic was cut on one side only and the increase occurred on that side alone this served as a useful control showing that the hyperaemia was not due to release of metabolites from

the traumatized tissue or any other factor connected with the operation other than the sympathetic denervation

In the case of two of the subjects operated upon for the hands preganglionic section was performed on one side and *postganglionic on the other (ganglionectomy)* as *Fig* 7 4 shows the results did not appear to differ Fig 7 5 shows that

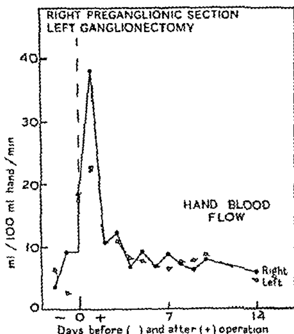


Fig 7 4 Changes in blood flow in the hands after sympathectomy by preganglionic section on one side and by ganglionectomy on the other The whereabouts of the sympathectomy made no difference to the circulatory changes (Walker Lynn and Barcroft 1950)

in muscle vessels too the rate of recovery of tone after preganglionic section appears to be much the same as that after ganglionectomy (Duff 1951)

Adson and Brown (1929) found that after sympathetic denervation the toes were warm for many days this was confirmed by our results (Fig 7 2) The fact that they remained warm in spite of the subsidence of the hyperaemia in the foot as a whole cannot at present be explained The finger tips are known to contain great numbers of A V anastomoses and

it may be that these regain relatively less tone than the vessels generally in the foot Another possibility is that of a greater heat loss from each millilitre of blood passing through the toes owing to the increased capacity of the veins after sympathetic

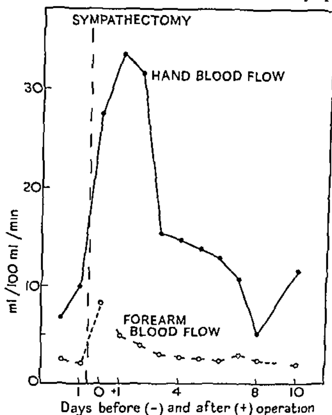


Fig 7 5 Records of the effect of sympathectomy on the blood flow in the forearm and hand
The maximum flow was recorded earlier in the forearm it was smaller and it subsided more quickly
This may have been due to slight differences in the behaviour of the blood vessel in muscle and skin (Duff 1951)

denervation (Goetz 1950) Or it may be that the digits remain warm because they cannot sweat

The vascular response first described in the hand and foot probably represents essentially the effect of sympathectomy on the cutaneous vessels The response of the vessels in the forearm probably that of skeletal muscle blood vessels has been

examined with the plethysmograph by Duff (19 1) The results obtained on forearms with normal blood vessels are shown in Fig 7 5 and the figure also shows the results obtained simultaneously in the hands of the same subjects The general resemblance is clear Duff described the following differences The maximum was reached sooner in the forearm than in the hand its extent was smaller and the regain of intrinsic tone was quicker The maximum was of the same order as that recorded after blocking the deep nerves to the forearm muscles (Chapter 1) Similar results were obtained in the calf by Dornhorst (1951) who found that the maximum calf blood flow occurred on the day of the operation

We must now turn to the explanation of the return of tone It is generally recognized that after section of a nerve the distal part undergoes an ordered process of destruction known as Wallerian degeneration These changes take place at much the same rate in all mammals (Young 1950) Cannon and Rosenbleuth (1949) have shown that the consequences of denervation extend beyond the distal neurones to the effector cells They do not die but they undergo very fundamental alterations in their way of life The striated the smooth the cardiac muscle cell and the gland cell are all affected The chief manifestation of this is their increased sensitivity to chemical stimulation It holds for excitation as well as for inhibition and it applies to stimulation by the chemical transmitters adrenaline and acetylcholine which act outside the cell and to stimulation by other drugs which only act after penetration Supersensitivity occurs to a less extent if the nerve supply is cut through the penultimate neurone

The facts have been aptly summarized by Cannon and Rosenbleuth (1949) in the law of denervation It runs

when in a functional chain of neurones one of the elements is severed the ensuing total or partial denervation of some of the subsequent elements in the chain causes a supersensitivity of all the distal elements including those not denervated and effectors if present to the excitatory or inhibitory action of chemical agents and nerve impulses the supersensitivity is greater for the links which immediately follow the cut neurones and decreases progressively for more distant elements

The known changes in the denervated cells which cause the

supersensitivity are very imperfectly understood They may affect among other things enzyme systems and the permeability of the cell wall to potassium and phosphorus (Lyman 1942 Friedlander Perlman and Chaikoff 1941) and to histamine

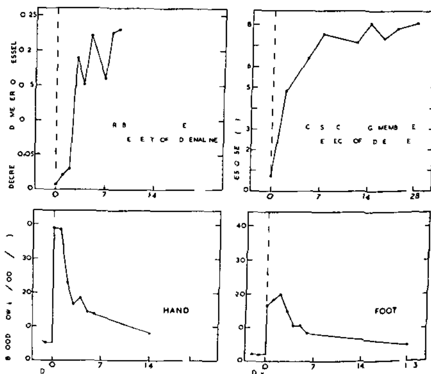


Fig 7 6 Results showing that the time relations for the devel pment of intrins c tone in the vessels of the han l an l foot after sympathectomy closely re emble those for the development of a lrenaline s ipersen ti ity i tl e rabbit ear ves els and nict tating membrane
Ir trinsic tone levelops at tl e same time as the phenomena l scribed by Cannon an l Ro nbleuth s law of lenervati n (*T j l ft* Hampel 193 *Top r ght* LeC mpte *1941*)

(Cannon and Rosenbleuth 1936) The permeability of capillaries may also be affected (Gabbe 1926 Engel 1940)

Many of these facts have been established for many years and have been the basis of attempts to explain how tone is regained The connection between the law of denervation and the regain of tone appears to us to be still more firmly estab lished by the experiments on the blood flow through the hand

and foot For as Fig 7 6 shows the rate of regain of tone is so remarkably similar to the rate of development of adrenaline supersensitivity after comparing these curves it is difficult to escape the conclusion that the events they represent must be very closely related Sympathectomy must start a chain of biophysical and biochemical events in smooth muscle which are manifested by supersensitivity and the regain of tone

The following hypotheses have been suggested to explain the return of tone

(1) It may be due to the arteries becoming supersensitive to circulating adrenaline (Freeman Smithwick and White 1934 Smithwick Freeman and White 1934 White Okelberry and Whitelaw 1936 Ascroft 1936)
(2) It may be due to supersensitivity to an unknown hormone (Grant 1935 LeCompte 1941)
(3) It may be the direct effect on the contractile process of intrinsic changes in the smooth muscle (Cannon 1937 Doupe 1943)

Those in favour of the adrenaline sensitivity theory have based their view principally upon experiments showing that sympathectomized vessels in man and animals are supersensitive to injected adrenaline and to the secretion of the suprarenal gland when excited by insulin or struggling That they are indeed supersensitive to adrenaline in some subjects has recently been shown with the plethysmograph by Duff (1952) and may be seen in Fig 7 7 However these findings are in themselves no proof that regain of tone is due to supersensitivity to circulating adrenaline since in the resting state there may not be sufficient in the blood to cause the vessels to contract This question might be settled by ascertaining if vessels that had regained tone could be reopened by an adrenergic blocking agent

Grant (1935) and LeCompte (1941) showed very clearly how the sympathectomized arteries of the rabbit s ear became supersensitive to an unknown constrictor substance It was not adrenaline or pituitrin since it was secreted in the adrenalectomized and in the hypophysectomized animal However there is no conclusive evidence for the presence of an active constrictor substance in the blood of a normal resting human being

The Late Changes

Paterson Ross (1946) has stated that the results of a well planned and correctly executed sympathectomy are permanent On the other hand Simmons and Sheehan (1939) and Haxton (1947) found that in many cases vasomotor and sudomotor reflexes returned The question of the completeness and permanence of sympathectomy is obviously important in both clinical and research work So we shall now describe tests performed on a large number of sympathectomized arms to assess the completeness of the denervation

Altogether 56 were studied (Barcroft and Hamilton 1948a b) Most of them had been operated upon for vascular disease In all cases the sympathetic path was cut through the preganglionic fibres (Smithwick s operation 1940) The interval between the operation and the performance of the test varied from 1 month to 6 years

The completeness of the sympathectomy was first assessed with the plethysmograph which gives rather more quantitative information about the blood flow than the finger temperature method used by the previous authors The principle of the test is that in normal subjects warming the body causes a central release of vasomotor tone which is manifested by flushing and increased blood flow in the extremities In sympathectomized ones the circulation in the extremities is not affected (Landis and Gibbon 1933) The test was carried out as follows (Fig 7 8) The blood flow in the hand was recorded at 5 minute intervals for a preliminary control period of half an hour The subject was then covered with two blankets and both his or her feet immersed to well above the ankles at 45° C Recording continued for an hour more Afterwards the blood flow at the end of the period of heating was divided by the initial resting blood flow the result was the heating ratio In the experiment shown in Fig 7 8 the heating ratio was 6 warming the body had increased the blood flow in the hand sixfold In a completely sympathectomized subject the heating ratio would have been approximately 1

The heating ratios of some normal hands are shown in Fig 7 9 In all of them warming the body caused a three to fivefold increase in the circulation The figure shows also the

results obtained on the 56 sympathectomized hands These are arranged from left to right in increasing order of interval of time between operation and testing All hands tested within six months of operation had heating ratios of about 1—i e

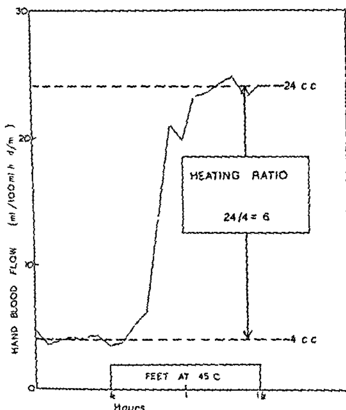


Fig 8 Vasomotor test for sympathetic vasomotor innervation of the hand

The hand blood flow is recorded before and during immersion of the feet in warm water to release sympathetic constriction The increase in flow or heating ratio is a useful index of sympathetic vasomotor activity (Barcroft and Hamilton 1948a)

reflex heating had no significant effect on their vessels In contrast to these early results many hands tested between one and six years after denervation had heating ratios considerably greater than 1—that is warming the body had elicited reflex vasodilatation

In many cases the test was repeated and instead of warming the body to release the vasoconstrictor tone the deep nerves were blocked (radial median and ulnar Chapter 1) The results of the two different methods were similar

Fortunately the state of the sympathetic paths could be assessed by another altogether different test a sudomotor test

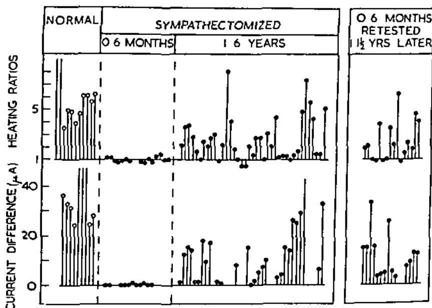


Fig 9 Results of vasomotor and sudomotor tests performed on 561 mb after sympathectomy arranged from left to right in order of time interval between operation and testing

Vasomotor and sudomotor reflexes were absent in limbs tested 6 months or less after operation but present in limbs tested 1–6 years after operation

The results show that the sympathetic re establishes connection with the blood vessels and sweat gland in the hand (Barcroft and Hamilton 1948a b)

The principle of this test is that the resistance to the passage of a current through the body lies almost entirely in the skin and is determined mainly by the activity of the sweat glands This in turn depends on nervous excitation mediated by the sympathetic (Richter 1946) The apparatus for testing the resistance of the skin consisted of a 4½ volt battery with one of the poles connected to an indifferent electrode and the other through a microammeter to a brass applicator with an insulated

handle (Haxton 1947) The test was carried out as shown in Fig 7 10 The indifferent electrode was strapped in the axilla The skin current over the pulp spaces of the thumb middle and little finger was measured at intervals of 5 minutes After a control period of half an hour the subject was warmed to induce maximal activity of the sweat glands and the ulnar nerve was blocked with 4 per cent procaine and adrenaline to prevent any impulses from reaching the little finger Skin current readings continued for another hour After the test the current that had passed through the little finger (control skin) at the end of the period of body warming was subtracted from the average of the currents that had passed through the thumb and middle finger (test skin) The result was the current difference In the experiment shown in Fig 7 10 owing to the relative moisture of the test skin caused by activity of the sympathetic sudomotor fibres there was a current difference of 24½ microamps In completely sympathectomized hands the current difference is approximately zero since there is no material difference in the amount of sweat in the test and control skin areas

The current differences of a number of normal hands are shown in Fig 7 9 in all of them there were quite large current differences The figure shows also the results obtained on the 56 sympathectomized hands They are arranged as before in order of increasing interval of time between operation and investigation and vertically below the corresponding results for the vasomotor test The results of the sudomotor test like those of the vasomotor one fall into two groups—those obtained on them six months after sympathetic denervation and those obtained a year or more after All hands tested within six months had very small current differences Many of the others however had quite large ones warming the body had caused sweating

Considering the results of both vasomotor and sudomotor tests it was clear that there was no evidence of any significant connection between the brain and the hand for several months after sympathectomy However a year or more after operation vasomotor and sudomotor reflexes were often present

Finally sixteen of the seventeen hands tested within six months of sympathetic denervation were retested 1–1½ years

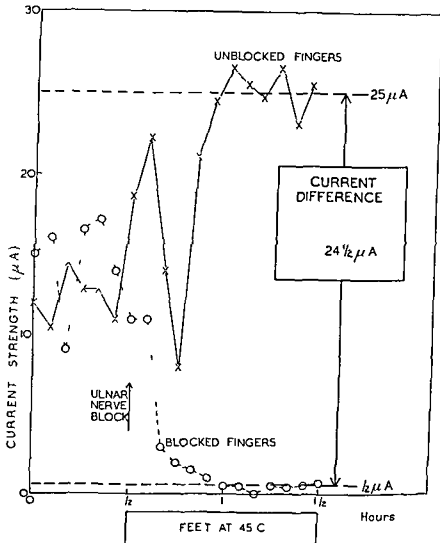


Fig 7 10 Sudomotor test for sympathetic innervation of the hand
The electrical conductivity is measured through
(1) The skin of the tips of the middle finger and thumb in which maximal activity of the sweat gland has been excited by warming the subject The results are averaged (test skin)
( ) The skin of the tip of the fifth finger which has been deprived of sympathetic activity by ulnar nerve block (control skin)
The difference between the conductivity of the test and control skins (current difference 1–2) is a useful index of sympathetic sudomotor activity (Barcroft and Hamilton 1948a)

later The results seen in Fig 7 9 showed that vasomotor *and sudomotor reflexes had returned to many of these hands*

A number of points need further comment In the first place the blood vessels of all the hands (seventeen) examined within six months of operation must have been to all intents and purposes completely sympathectomized by cutting the rami communicantes of T2 and T3 and the sympathetic chain between T3 and T4 as was done at operation in every case *The existence of other paths that would have been left intact* by these sections is suggested by the work of Kuntz Alexander and Furcolo (1938) van Buskirk (1941) Kirgis and Kuntz (1942) Skoog (1947) Ray and Console (1948) and Boyd and Monro (1949) However as far as the blood vessels of the hands we examined are concerned such paths cannot have been of much importance We cannot speak with such assur*ance about the completeness of the sympathetic denervation* of the sweat glands in the first place our apparatus was not very sensitive and in the second we were concerned only with the glands in the skin of the finger tips

It would be of great interest to know how the new connection established by the sympathetic compares with the original as regards function No doubt there will be great differences from *one individual to another It is worth examining the* meagre data available The figures in Table V suggest that *in most subjects the new connection functions poorly* The table shows that 1–5 years after sympathectomy the hands

TABLE V

	Sympathectomized		Normal
	1–6 months	1–5 yrs	
Average heating rate	1 0	8	9 5
Average hand blood flow during body warming (ml per 100 ml per minute)	9 1	11 1	23 1
Effect of operation on frequent vasospastic attacks—			
cured		18	
relieved		14	
unaltered		4	

resembled completely sympathectomized ones rather than normal ones both as regards their heating ratios and blood flows during reflex vasodilatation (Hamilton 1947). This suggests a deficient innervation. However it may have been rather better than would appear from the figures for vascular disease would have slightly restricted the capacity of the vessels to dilate. There is another reason for thinking that little function returns. It concerns the beneficial effect of the sympathetic denervation on the vascular disorder. Of 36 limbs sympathectomized for frequent vasospastic attacks and first seen 1–5 years later 18 had had no recurrence since the operation. Yet to many of them the reflexes had returned. This too suggests that the reconnection was a poor one.

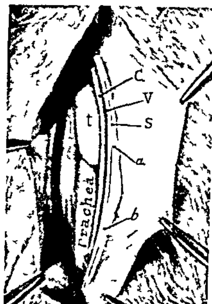


Fig 7.11 Drawing showing how regenerating nerve fibres bridged a gap of $\frac{4}{16}$ inch in a cat's right cervical sympathetic chain.
The nerve ends *a*, *b* of the sympathetic nerve S are slightly thickened and are joined by numerous strands. *t* thyroid gland; C common carotid artery; V vagus nerve (Lee 1930).

How the reconnection in the sympathetic path comes about cannot at present be explained. *There are two* possibilities. The development of a new path in the rami communicantes above the level of T2 and regeneration of the cut fibres across a gap of about an inch. The former has been described in the cat by Geohegan and Aidar (1942). Following interruption of preganglionic pathways to the forepad preganglionic pathways developed higher up from roots which normally contribute nothing to the forepad. As regards regeneration the powers possessed by the sympathetic in animals at any rate seem to be very much greater than those with which somatic sensory and motor fibres are endowed. An experiment of Lee's (1930)

is worth quoting Lee cut a cat s cervical sympathetic and fixed the ends so that they were separated by an inch of muscle After 27 days stimulation of the proximal end excited the typical retraction of the nictitating membrane and enlargement of the pupil Stimulation of the tissue between the nerve ends showed that the regenerated fibres had taken a course partly through the muscle and partly round it Histological sections confirmed that regeneration had occurred The results of another of Lee s experiments are shown in Fig 7 11

REFERENCES

Adson W A and Brown C F (1929) *Surg Gynec Obstet* **48** 577
Ascroft P B (1936) *Brit J Surg* **24** 78
Barcroft H and Hamilton G T C (1948a) *Lancet* **1** 441
—— (1948b) *Lancet* **2** 7 0
Barcroft H and Walker A J (1949) *Lancet* **1** 1035
Boyd J D (1950) Personal communication
Boyd J D and Monro P A G (1949) *Lancet* **2** 892
Buskirk C van (1941) *Arch Surg Chicago* **43** 49
Cannon W B (1937) *Amer Heart J* **14** 383
Cannon W B and Rosenbleuth A (1936) *Amer J Physiol* **116** 408
—— (1949) *The Supersensitivity of Denervated Structures* New York Macmillan
Dornhorst A C (1951) Unpublished observations
Doupe J (1943) *J Neurol Psychiat* **6** 97
Duff R S (1951) *Clin Sci* **10** 529
—— (1952) *J Physiol* **117** 415
Engel D (1940) *J Physiol* **99** 161
Freeman N E Smithwick R H and White J C (1934) *Amer J Physiol* **107** 529
Friedlander H D Perlman I and Chaikoff I L (1941) *Amer J Physiol* **132** 24
Gabbe E (19 6) *Z ges exp Med* **51** 728
Geohegan W A and Aidar O J (1942) *Proc Soc exp Biol N Y* **50** 36
Goetz R H (1950) *Circulation* **1** 6
Goltz F and Freusberg A (1874) *Pflug Arch ges Physiol* **9** 174
Grant R T (1935) *Clin Sci* **2** 1
Grant R T and Pearson R S B (1938) *Clin Sci* **3** 119
Grayson J (1948) M D Thesis University of Manchester
Greenfield A D M Kernohan G A Marshall R J Shepherd J T and Whelan R F (1951) *J appl Physiol* **4** 3
Hamilton C T C (194) M D Thesis Queen s University Belfast
Hampel C W (1935) *Amer J Physiol* **111** 611
Haxton H A (1947) *Brit J Surg* **35** 69
Hermann H and Guiran J B (1934) *Bull Histol tech micr* **11** 381
Kirgis H D and Kuntz A (1942) *Arch Surg Chicago* **44** 9

Kuntz A Alexander W F and Furcolo C L (1938) *Ann Surg* **107** 25

Landis E M and Gibbon J H (1933) *Arch intern Med* **52** 785

LeCompte P M (1941) *Amer J Physiol* **135** 43

Lee F C (1930) *Res Publ Ass nerv ment Dis* **9** 417

Lewis T and Landis E M (1929) *Heart* **15** 151

Lyman C P (1942) *Amer J Physiol* **137** 392

Lynn R B and Barcroft H (1950) *Lancet* **1** 1105

McDowall R J S (1938) *The Control of the Circulation of the Blood* London Longmans

Ray B S and Console A D (1948) *J Neurosurg* **5** 23

Richter C P (1946) *J Neurosurg* **3** 181

Ross J P (1946) *Brit med J* **1** 1

Simmons H T and Sheehan D (1939) *Brit J Surg* **27** 234

Skoog T (1947) *Lancet* **2** 457

Smithwick R H (1940) *Ann Surg* **112** 1085

Smithwick R H Freeman N E and White J C (1934) *Arch Surg Chicago* **29** 759

Telford E D (1935) *Brit J Surg* **23** 448

Walker A J Lynn R B and Barcroft H (1950) *St Thom Hosp Rep* **6** 18

White J C Okelberry A M and Whitelaw G P (1936) *Arch Neurol Psychiat Chicago* **36** 1251

Wilkins R W and Eichna L W (1941) *Bull Johns Hopk Hosp* **68** 425

Young J Z (1950) Personal communication

CHAPTER 8

THE ACTION OF ADRENALINE AND NORADRENALINE ON THE CIRCULATION IN THE SKIN

Both adrenaline and noradrenaline cause pallor of the face in man This effect is usually attributed to the direct constrictor action of the amines on the cutaneous vessels However a more detailed study of the problem reveals certain interesting facts in regard to the action of these substances on the vascular system in the skin

Although visual inspection of the skin colour may indicate its vascular state objective studies of the skin surface are unsatisfactory if we are attempting to follow rapid changes in skin blood flow Skin temperature measurements are of little use in such investigations because the change in surface temperature lags behind an alteration in blood flow by an appreciable interval As an extreme example of this it may be shown that when the blood flow in a limb is completely occluded by a pressure cuff there is only a gradual fall in skin temperature Also if the blood flow increases from a state of moderate dilatation to one of full dilatation only a small rise of skin temperature occurs whereas changes from moderate dilatation to a lower flow may be accompanied by a considerable fall in skin temperature (Lewis 1927) Heat elimination (Cooper et al 1950) is also unsatisfactory as it reflects average changes which have occurred over a period of time The use of the hand or foot plethysmograph avoids the response lag and gives an accurate picture of the variation in flow It has the disadvantage however that measurements of blood flow are made on a specialized skin site and on a structure containing some muscle Nevertheless the blood flow changes in the hand and foot reflect predominantly alterations in the skin vessels (Abramson and Ferris 1940)

We will consider in detail the changes in blood flow in the hand during and after infusions of adrenaline or noradrenaline Precautions have to be taken lest the response is due to chance

for the hand blood flow undergoes considerable spontaneous variation and is also influenced by emotional stimuli (Wilkins and Eichna 1941)

The Vasoconstrictor Action of Adrenaline and Noradrenaline

In order to compare the constrictor properties of these substances on the skin blood vessels infusions were made into the brachial artery thus avoiding any central effects which these substances might cause Because of the experiences gained in an earlier investigation infusion rates of $\frac{1}{4}$ $\frac{1}{8}$ $\frac{1}{16}$ and $\frac{1}{32}$ μg per minute were used Table VI summarizes the findings There appears to be little difference in the constrictor activity of the two substances This is somewhat surprising for the facial pallor caused by adrenaline is always more evident than the pallor resulting from a similar amount of noradrenaline What is the explanation of this apparent anomaly? We recognize the preponderance of skin over muscle in the tissues of the hand but some muscle is present

TABLE VI

The hand blood flow response to intra arterial infusions of adrenaline and noradrenaline[1]

Dose μg/min	Average of 10 subjects Average blood flow (ml/100 ml/min) *Before*	*During*	*After*
Adrenaline			
$\frac{1}{32}$	12.9	12.0	13.1
$\frac{1}{16}$	10.3	8.[illegible]	10.9
$\frac{1}{8}$	12.1	[illegible].0	10.9
$\frac{1}{4}$	9.6	2.9	8.6
Noradrenaline			
$\frac{1}{32}$	9.8	8.0	7.3
$\frac{1}{16}$	10.2	7.[illegible]	10.0
$\frac{1}{8}$	11.1	4.4	9.3
$\frac{1}{4}$	10.2	2.7	7.7

[1] Intra arterial infusions of adrenaline at $\frac{1}{4}$ μg/min did not cause any vasoconstriction in the hand of Duff's experiments Fig 7 In this respect they differ from those seen in Table VI This discrepancy is probably due to small differences in the vascular responses of the subjects and in the procedures and analytical methods It is unlikely that the conclusions of either investigator are incorrect

(Abramson and Ferris 1940) Therefore the blood flow through the hand is the sum of both skin and muscle blood flow Now in small doses as used in this study adrenaline causes a transient dilatation in muscle blood vessels followed by a return to the resting value whereas noradrenaline causes a powerful vasoconstriction (Chapters 3 and 4) Therefore doses of adrenaline which reduce the blood flow to say 25 per cent of its resting value accomplish this almost entirely by a skin vasoconstriction while noradrenaline reduces the muscle blood flow in addition to decreasing the skin flow Therefore one can conclude that adrenaline is stronger in constrictor action on skin vessels than noradrenaline which is in keeping with the impression gained from visual inspection

The Central Dilator Action of Adrenaline

After intravenous infusions of moderate amounts of adrenaline in man flushing of the skin of the face frequently occurs This had been attributed to reactive hyperaemia following the vasoconstriction caused by the action of adrenaline on the blood vessels It appeared to have its counterpart in the vessels of the hand for in a small series of subjects it was clear that the hand blood flow increased after the intravenous infusion was discontinued The after dilatation was not seen in sympathectomized limbs nor after intrabrachial infusions in normal ones (Swan 1950) As this seemed to be of some importance the matter was more carefully examined (Swan 1951)

The effect of intravenous infusions of adrenaline and noradrenaline on the hand blood flow was studied using a plethysmograph filled with water at 33 C The room temperature was maintained at 21 C Under these conditions subjects chosen at random from a class of medical students showed a surprisingly consistent response to 20 μg adrenaline per minute and to 20 μg noradrenaline per minute Intravenous infusions of either of these substances for 3 minutes caused a decline in blood flow for approximately the duration of the infusion In the case of noradrenaline the blood flow returns to about the previous level after the infusion is discontinued With adrenaline however the phase of constriction is succeeded by an increase in blood flow which occurs with sufficient frequency

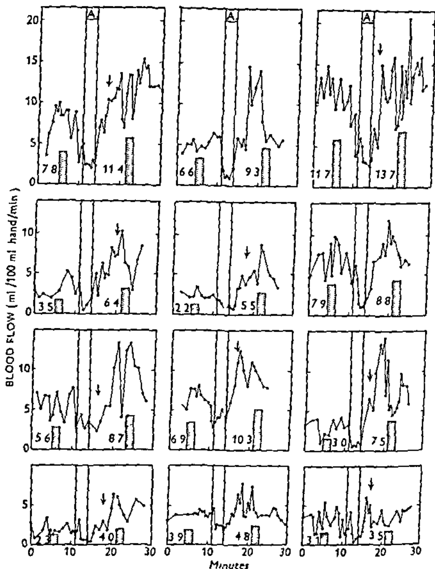


Fig 8 1 Results showing hyperaemia in the hand and flushing of the face following intravenous infusions of adrenaline

The shaded blocks represent (half scale) the average flows recorded in the periods 0–10 and 17–27 min 3 min infusions at 20 µg/min The arrows denote the beginning of flushing (Swan 1951)

not to be due to chance. Twelve successive experiments in which infusions of 20 μg adrenaline were given to normal medical students are depicted in Fig 8 1. Table VII gives a summary of the findings in a number of these experiments.

It must be pointed out that in the experiments mentioned above the adrenaline and noradrenaline affected the tissues besides the vessels in the hand and alterations in cardiac output, blood pressure and heart rate occurred. It was therefore decided to carry out a similar series of experiments using the technique of brachial artery infusion and by giving a dose sufficient to cause a powerful constriction. *By this method* a study of the direct effect of adrenaline and noradrenaline on the vessels of the hand could be made while the central effects were avoided. Smaller amounts of adrenaline were used for the drug was not diluted in the general circulation as during intravenous infusions. The findings are shown in Fig 8 2. During the period of infusion the hand flow is much reduced. No after dilatation was observed in these experiments or in the experiments described in the first section of this chapter in which smaller doses were infused intra arterially.

TABLE VII

The hand blood flow response to infusions

(Each group is the average of the ten most recent experiments)

		Average blood flow (ml /100 ml hand min)			Significance of any increase after the infusion
		Before	*During*	*After*	
Normal limbs					
1 Intravenous					
Adrenaline	10 μg	8 4	4 4	8 8	P = 5
	20 μg	7 8	2 8	9 8	P < 001
Noradrenaline	10 μg	8 1	3 8	9 1	P = 2
	20 μg	8 0	3 1	7 8	
2 Intra arterial adrenaline	½ μg	7 1	1 0	4	P = 5
Sympathectomised					
Intravenous	10 μg	7 6	2 6	7 1	– 5 subjects
Adrenaline	20 μg	6 6	1 8	5 9	– 5 subjects

Room temperature 21 C. Plethysmograph water temperature 33 C. 3 minute infusions.

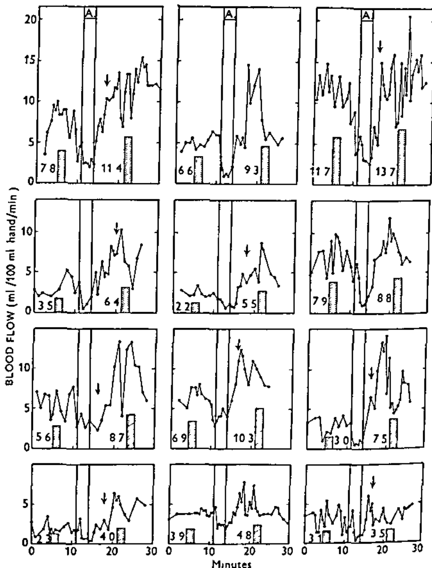


Fig 8 1   Results showing hyperaem a n the han l and flushing of tl e face f llowing intravenous infusions of adrenaline
The shaded blocks represent (half scale) the average flows recorded in the periods 0–10 and 17–‸7 min   3 min infusions at 0 µg /min   The arrows denote the beg nning of flushing   (Swan 1951)

While the noradrenaline flush is of rather a dusky tint the adrenaline flush is bright and intense and is accompanied by a sensation of warmth which spreads over the body—but is chiefly experienced in the face and hands

It is clear that the flushing has its counterpart in the hand blood flow response As we have pointed out there is a significant increase in blood flow in the hand following intra venous infusions of 20 μg adrenaline per minute for 3 min The changes following noradrenaline and smaller doses of adrenaline are not significant What is the cause of this increased blood flow? A change in blood flow may result from an alteration in the arterial pressure into the organ or from a change in the vascular resistance in the blood vessels themselves Increase in arterial pressure could not account for the increase in blood flow after adrenaline since blood pressure observations make it clear that there is no increase Moreover the observations of Green et al show that flushing of the face coincides with a phase of hypotension There fore it is reasonable to consider that there is in fact a dilatation of the blood vessels after the termination of the adrenaline infusion This dilatation might result from the direct action of substances on the blood vessels or it might be due to changes in the nervous influences which regulate the vessels The first of these alternatives seemed likely on the grounds that the skin vessels had been constricted for the duration of the infusion and dilator metabolites might have accumulated locally But this possibility cannot be the explanation for as we have pointed out earlier intra arterial infusions are not followed by dilatation It might be argued that in the intravenous experiments the adrenaline liberated a dilator substance from some central organ into the general circulation and that this substance was then borne by the blood to the skin where it caused dilatation To test this hypothesis the response to intravenous adrenaline was studied in sympathectomized sub jects Fig 8 3 shows that no dilatation followed the infusion By elimination we may conclude that the dilatation which follows intravenous adrenaline in normal subjects is due to alteration in the nervous control of the blood vessels We may be more precise for Arnott and Macfie (1948) have shown that the skin of the little finger does not contain dilator nerve fibres

It is probable that the whole hand is similar Therefore the adrenaline dilatation is due in fact to an inhibition of sympathetic constrictor nerve impulses How may this inhibition of constrictor tone come about ? It is unlikely to be due to a depressor reflex because it frequently coincides with a phase of hypotension But there is considerable evidence to show that adrenaline affects autonomic transmission This has been shown in animals following the injection of very small doses of

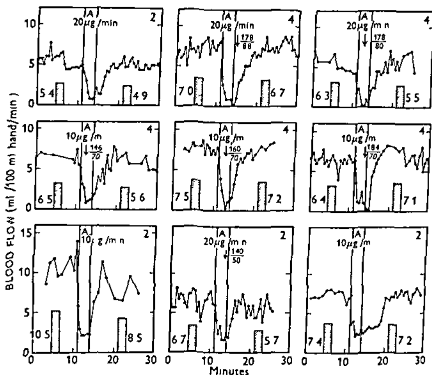


Fig 8 3 Results showing that intravenous adrenaline infusions in sympathectomized subjects are not followed by hyperaemia in the hand

The hyperaemia after intravenous infusions in normally innervated hand (Fig 8 1) cannot be due to the liberation of a vasodilator substance into the general circulation and its subsequent action on the hand vessels

It is probably due to a central dilator action of adrenaline mediated by the sympathetic and abolished by sympathectomy

The shaded blocks represent (half scale) the average flows recorded in the period 0–10 and 17–27 min 3 min intravenous infusions The arrow indicated the time at which the maximal blood pressure given on the diagram was recorded The number of limbs sympathectomized including the test limb is shown in the top right hand corner (Swan 19 1)

adrenaline and after reflex stimulation of the sympathetic supply to the adrenal gland (Marrazzi 1939a Bulbring and Burn 1942 Posternak and Larrebee 19 0) We may con clude that the after dilatation seen in normal limbs is due to direct depression of vasoconstrictor tone probably in the sympathetic ganglia

Finally—what is the significance of this mechanism? We may consider it either as part of the emergency reaction (Can non 1929) or as a protective mechanism (Marrazzi 1939b) or as a harmful mechanism (Bulbring and Burn 1942) As regards the third we feel that it is unlikely that under normal conditions sufficient amounts of adrenaline are liberated to cause a harmful hypotensive state also we consider that adrenaline shock depends on an inability of the blood vessels to respond to pressor hormones and this should not result from ganglionic blockade or depression of nervous vasocon strictor tone The inhibition of vasomotor tone may on the other hand do much to mitigate against excessive rises of blood pressure thus acting as a protect on against harmful effects

REFERENCES

Abramson D I and Ferris E B (1940) *Amer Heart J* 19 541
Arnott W M and Macfie J M (1948) *J Physiol* 107 233
Barclay J A Cooke W T and Kenney R A (1947) *Amer J Physiol* 151 621
Bulbring E and Burn J H (1942) *J Physiol* 101 289
Cannon W B (1929) *Bodily Changes in Pain Hunger Fear and Rage* Appleton N Y
Cooper K E Cross K W Greenfield A D M Hamilton D and Scarborough H (1950) *Clin Sci* 8 217
Green D M Johnson A D Lobb A and Cusick G (1948) *J lab clin Med* 33 332
Hyman A and Mencher W H (1943) *J Urol* 49 [illegible]
Lewis T (1927) *Blood Vessels of the Human Skin and Their Responses* Shaw London
Marrazzi A S (1939a) *Science* 90 2[illegible]
—— (1939b) *J Pharmacol* 65 39[illegible]
Posternak J M and Larrebee M C (19 0) *Bull Johns Hopk Hosp* 87 144
Swan H J C (19 0) *J Physiol* 111 [illegible]
—— (1951) *J Physiol* 112 426
Wilkins R W and Lechna [illegible] W (1941) *Johns Hopk Hosp Bull* 68 4[illegible]0

CHAPTER 9

THE ACTION OF ADRENALINE AND NORADRENALINE ON THE GENERAL CIRCULATION

The presence of both adrenaline and noradrenaline in the human body makes it of great interest to compare their actions on the general circulation The more so since they differ remarkably

The effects of intravenous infusions have been studied by Goldenberg Pines Baldwin Greene and Roh (1948) and by Barcroft and Starr (1951) Small differences in the findings may be explained by the fact that the rates and durations of the infusions differed in the two investigations Both authors recorded the changes in arterial blood pressure and cardiac output Goldenberg et al used the cardiac catheterization technique Barcroft and Starr the ballistocardiograph

The effects of infusions at the rate of 10 μg per minute may be summarized as follows First as regards symptoms and signs With adrenaline an early sensation was a curious feeling of expectancy with a transient mild tingling all over the body Then there followed an increase in depth and rate of respiration and the subjective symptoms associated with hyperventilation It was possible to hold a moderate inspiration for only about 10 15 sec About 10 sec after the start of respiratory symptoms the heart rate increased—but this increase might not be noticed by the subject for several seconds Gradually the force of beat increased for a further ½ min after which the rate frequently fell back to a few beats above its resting value The subject remained aware of the forcefulness of the heart beat Shortly after the start of cardiac symptoms a feeling of fatigue spread into the back—and into both legs A coarse tremor of the extremities was common After the first two minutes the symptoms diminished very considerably

With noradrenaline the symptoms were very different The feeling of anxiety or expectancy was absent in most subjects although two subjects reported apprehension with noradrena

line and no psychical symptoms with adrenaline Respiration was increased but there was no palpitation fatigue or muscle tremor Infusion of both amines caused a facial pallor but adrenaline to a greater extent than noradrenaline

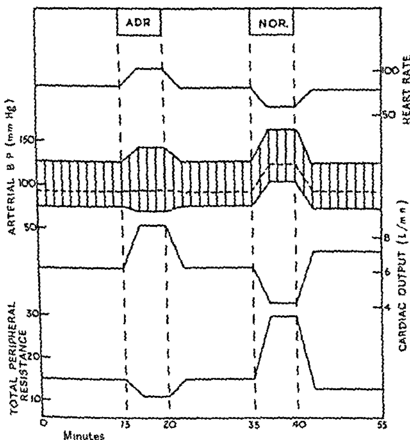


Fig 9 1 Diagrammatic representation of the effects of intravenous infusions of adrenaline and of noradrenaline on the heart rate arterial blood pressure cardiac output and total peripheral resistance

(The initial transient decrease in the arterial blood pressure which occurs during infusions of adrenaline (Fig 9 3) is not shown)

Other changes are shown diagrammatically in Fig 9 1 Adrenaline caused tachycardia which like the *palpitations* usually subsided though in this case not altogether during the course of the infusion (see also Hume 1927) Noradrenaline

on the other hand caused bradycardia Before this curious paradox can be discussed the other circulatory changes in Fig 9 1 must be described Adrenaline did not have much effect on the mean blood pressure it raised the systolic but it either did not affect or lowered the diastolic Noradrenaline had much greater effect because it raised both the systolic and diastolic pressures (see also Barnett et al, 1950) Adrenaline increased the cardiac output whereas noradrenaline either did not affect it (Goldenberg et al) or decreased it (Barcroft and Starr) The changes in the total peripheral resistance were calculated from the cardiac outputs and mean blood pressures Adrenaline decreased the overall resistance whereas noradrenaline increased it That is adrenaline acted as an overall vasodilator noradrenaline as an overall vasoconstrictor

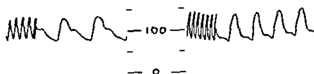
To return to the explanation of the different effects of the two substances on the heart rate Both excite the isolated and atropinized hearts (West 1947 Ahlquist 1948) adrenaline more so than noradrenaline But in the human subject this action will be opposed by increased vagal inhibitory tone reflexly excited by the rise in the mean blood pressure This rise is less with adrenaline than with noradrenaline The difference in their actions on the heart rate in man is therefore probably due to the predomination of local excitation with adrenaline and of reflex inhibition with noradrenaline

The different actions of the two substances on the diastolic pressure is probably due to their different effects on the peripheral resistance During infusions of adrenaline in spite of the tachycardia and increased output the blood probably passes so rapidly through the peripheral resistance that there is time for the pressure to fall precipitately between two successive heart beats With noradrenaline however although there is bradycardia and perhaps decreased output the escape of the blood from the constricted arteries is slow and the change in pressure during diastole is comparatively small

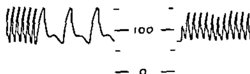
Studies of the arterial pulse contour changes are in accord with these observations Using a low displacement capacitance manometer Peterson Duff and Swan (1950) recorded the changes in pulse contour during infusions of adrenaline or noradrenaline Fig 9 2 is typical of their findings

In the case of adrenaline it is clear that the increased pulse

ADRENALINE
10 μg/min

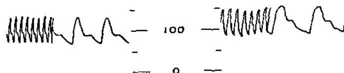


Before | $1\frac{3}{4}$ min after start



Just before end of 10 min infusion | 17 min after end of infusion

NORADRENALINE
10 μg/min



Before | 2 min after start



10 min after start

Fig 9.— Tracings of the arterial blood pressure recorded with a Lilly intra-arterial capacitance manometer during intravenous infusions of adrenaline and noradrenaline

Adrenaline: the increased pulse pressure and pulse rate signify increase in stroke and minute volume; the absence of a corresponding rise in the mean blood pressure signifies peripheral vasodilatation

Noradrenaline: the decreased pulse pressure and rate signify decrease in stroke and minute volume; the rise of mean blood pressure signifies peripheral vasoconstriction

pressure and pulse rate signify increased stroke volume and *increased cardiac output and the absence of a* corresponding rise in the mean blood pressure signifies peripheral vasodilata tion In the case of noradrenaline the decreased pulse pressure and pulse rate signify decreased stroke output and minute volume, and the rise of the mean blood pressure signifies peripheral vasoconstriction

To turn now to the whereabouts in the peripheral vascular system of the vasodilatation caused by adrenaline In what parts of the body is its action so different from that of the other substance ? Evidently not in the skin where both cause pallor Fortunately in man the circulations through most of the internal organs can be studied individually and the results show that the blood flow through the liver kidneys skeletal muscles and brain accounts for most of the output

Bearn Billing and Sherlock (1951) have described the effects *of the two hormones on the liver blood flow They used the* bromsulphalein (BSP) dye method The principle is as follows The dye is infused intravenously at a known rate the liver abstracts it from the blood at the same rate and excretes it in the bile The liver flow is calculated on the Fick principle from the rate of hepatic uptake (infusion rate) and the differ ence in the amounts of dye in the blood entering and leaving the liver (estimated in samples taken by arterial puncture and by hepatic venous catheterization) (Bradley Ingelfinger Bradley and Curry 1945) Bearn et al found that adrenaline increased the liver blood flow by about 100 per cent nor adrenaline did not materially alter the liver blood flow

The circulatory changes in the kidneys have also been studied Barclay Cooke and Kenney (1947) measured the renal plasma flow in eight subjects before and during 25–40 minutes intravenous infusion of adrenaline at rates of infusion varying from 0 5 to 10 μg per minute Constriction occurred in every subject the average decrease in flow being 40 per cent They were not concerned with the effect of noradrenaline which *was examined later by Barnett Blacket Depoorter,* Sanderson and Wilson (1950) It too caused constriction but apparently not so much as adrenaline since even with more than double the rate of infusion (20 30 μg per minute) the average decrease in flow in six subjects was only 20 per cent

The blood flow through the skeletal muscles probably accounts for another large fraction of the cardiac output at rest It will be remembered that after the transient vasodilatation in the forearm had passed off the blood flow remained approximately doubled (Allen et al 1946 Chapter 3) This was due to increase in blood flow through the muscles which must have been at least doubled In spite of the rise in general blood pressure intravenous infusions of noradrenaline do not increase the blood flow through muscle (Duncanson Stewart and Edholm 1949 Barcroft and Konzett 1949 Barnett et al 1950)

One of the large individual circulations is that through the brain The effects on it of adrenaline and of noradrenaline have been studied by King Sokoloff and Wechsler (1952) by the nitrous oxide and internal jugular venous blood sampling method Adrenaline increased the flow by approximately 20 per cent Noradrenaline caused constriction the average decrease in flow was 10 per cent

The changes in the different organs have been collected together in Table VIII and afford independent evidence not inconsistent with the findings previously described namely that adrenaline stimulates the cardiac output whereas noradrenaline does not They show that the overall vasodilator action of adrenaline is essentially due to its effect on the circulations in the liver and skeletal muscles

TABLE VIII

	Before	*During*			
	Adrenaline or Noradrenaline	Adrenaline		Noradrenaline	
	ml /min	ml /min	change	ml /min	change
Liver	1500	3000	+100	1500	0
Kidney	1500	900	−40	1200	−20
Skeletal muscles	1000	2000	+100	1000	0
Brain	750	900	+20	67	−10
	4750	6800	40	43[illegible]	−8

Finally it is of interest to compare the actions of the two amines on the blood pressure in man the cat the dog and the rabbit *It will be seen that differences still need to be explained* In animal experiments the hormones have usually been injected and not infused so that the corresponding effects

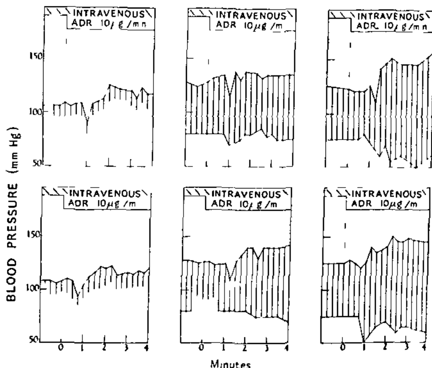


Fig 9 3 Experiments showing that the first effect of intravenous infusions of adrenaline on the human arterial blood pressure is to cause a small transient decrease

The blood pressure records were made every ¼ min by the auscultatory method (Allen Barcroft and Edholm 1946)

in man will be those taking place at the very beginning of an infusion before the establishment of equilibrium Careful measurement of the human arterial blood pressure by the auscultatory method usually reveals a small transient decrease before the sustained rise This may be seen in Fig 9 3 This transient decrease is readily displayed by the intra arterial manometer (Barnett et al) In this connection it is worth noting that infusions of adrenaline into a normal subject

never cause a sustained fall in pressure however great the dilution The transient fall in the human blood pressure probably corresponds to the fall seen following the injection of small doses in the cat (Cannon and Lyman 1912) and dog (Hoskins and McClure 1912 Lands Luduena Ananenko and Grant 1950) This is apparently unobtainable in the rabbit (Cannon and Lyman) With noradrenaline the situation is different In man the capacitance manometer shows that it causes a simple rise in pressure (Barnett et al) this is so in the cat too (Meier Gross and Eichenberger 1949) but oddly enough noradrenaline causes a fall in pressure in the dog (Lands et al) As far as we are aware the response in the rabbit has not been studied The explanation of these differences though of great fundamental interest is not at present known

REFERENCES

Ahlquist R P (1948) *Amer J Physiol* **153** 586

Allen W J Barcroft H and Edholm O G (1946) *J Physiol* **105** 255

Barclay J A Cooke W T and Kenney R A (1947) *Amer J Physiol* **151** 621

Barcroft H and Konzett H (1949) *J Physiol* **110** 194

Barcroft H and Starr I (1951) *Clin Sci* **10** 295

Barnett A J Blacket R B Depoorter A F Sanderson P H and Wilson G M (1950) *Clin Sci* **9** 151

Bearn A G Billing B and Sherlock S (1951) *J Physiol* **115** 430

Bradley S E Ingelfinger F J Bradley G P and Curry J J (1945) *J clin Invest* **24** 890

Cannon W B and Lyman H (1912) *Amer J Physiol* **31** 376

Duncanson D Stewart T and Edholm O G (1949) *Fed Proc* **8** 37

Goldenberg M Pines K L Baldwin E de F Greene D G and Roh C E (1948) *Amer J Med* **5** 792

Hoskins R E and McClure C W (1912) *Arch intern Med* **10** 343

Hume W F (19_) *Quart J Med* **21** 459

King D Sokoloff L and Wechsler R L (1952) *J clin Invest* **31** 275

Lands A M Luduena F P Ananenko E and Grant J I (1950) *Arch int Pharmacodyn* **83** 602

Meier R Gross F and Eichenberger E (1949) *Helv physiol pharmacol Acta* **7** 230

Peterson I H Duff R S and Swan H J C (1950) Unpublished observations

West G B (1947) *J Physiol* **106** 418

CHAPTER 10

ADRENERGIC BLOCKADE

In 1906 Dale found that large doses of preparations of ergot of rye paralysed the excitor function of the sympathetic nerves and also of adrenaline These observations were the basis of the considerable volume of work on adrenergic blockade and adrenergic blocking agents which has been carried out since then Adrenergic agents are the natural amines adrenaline and noradrenaline which induce the responses of the great majority of the sympathetically innervated effector cells Adrenergic blocking agents are those substances which specifically inhibit certain effects of adrenaline noradrenaline and sympathetic nerve stimulation The terms sympatholytic and adrenolytic should not be used for in general neither nerve ending nor mediator nor effector cell is lysed by these agents (Nickerson 1949) It should also be clear that adrenergic blockade refers to an action at the neuro effector junction that is a peripheral effect other actions on the efferent vasomotor pathway are by definition not part of this topic Nevertheless many adrenergic blocking agents cause vascular changes not due to their adrenergic blocking properties and we must endeavour to distinguish between these effects and true adrenergic blockade

There are four main groups of adrenergic blocking agents and in this chapter we will consider their action in man so far as it is at present known The effects of the alkaloids of ergot will be discussed in rather more detail than the other substances not only because we have invest gated them to a greater extent than the other agents but also because we may make certain generalizations which are applicable to all adrenergic blocking agents to varying degrees

1 *Hydrogenated Alkaloids of the Ergotoxine Group*

Although the anti adrenaline properties of the ergot extracts was recognized in 1906 the toxic effects of vasoactive doses prevented any serious investigation of the circulatory effects of ergot in man The principle of ergot which possessed the

greatest vascular activity (ergotoxine) also caused the most adverse side effects Stoll and Hoffman (1943a) showed that ergotoxine is made up of three separate alkaloids ergocornine ergocristine and ergocryptine The same workers (1943b) found that the lysergic acid molecule which is a component of each alkaloid could be hydrogenated to form new and stable substances These compounds known as dihydroergocornine dihydroergocryptine and dihydroergocristine (the dihydro alkaloids) were much less toxic than the natural alkaloids yet retained certain anti adrenaline properties

Because of the diminished toxicity the dihydroalkaloids were extensively investigated in man Dihydroergocornine (DHO 180) was studied by Bluntschli and Goetz (1947) Freis Stanton and Wilkins (1948) and others Less attention was given to the effects of mixtures of the dihydro alkaloids or to the effects of dihydroergocryptine or dihydroergocristine probably because dihydroergocornine displayed the greatest vascular activity The majority of these investigators made little attempt to interpret the action of the dihydro alkaloids describing many effects as evidence of the sympatholytic or adrenolytic properties of the compounds It is clear that not all of these effects would come within the more rigid definition of adrenergic blockade set out at the beginning of this chapter

Barcroft Konzett and Swan (1951) investigated the effect of dihydroergocornine and of a mixture of equal parts of the three dihydro alkaloids (Hydergine) on the human peripheral circulation They measured peripheral blood flow with the plethysmograph and found that either dihydroergocornine or Hydergine infused intravenously caused an increase in the blood flow in the hand and foot in all of ten normal subjects Fig 10 1 is from their paper This confirmed the observations of Goetz (1949) who measured the finger blood flow and Hayes et al (1949) who measured the blood flow in the whole limb Barcroft et al found little change in the calf blood flow in normal subjects

The cause of the dilatation in the hand and foot was considered Goetz (1949) had concluded that the dilatation was due to central inhibition of sympathetic vasoconstrictor tone and not to peripheral adrenergic blockade but his evidence did not exclude an adrenergic blocking effect Goetz concluded

that the dilatation seen in normal limbs was due to a central depression of vasoconstrictor tone because sympathectomized limbs fail to dilate He assumed that if the alkaloids dilated normal vessels by a peripheral action they should also cause dilatation in sympathectomized vessels This does not necessarily follow for a substance which blocks the adrenergic

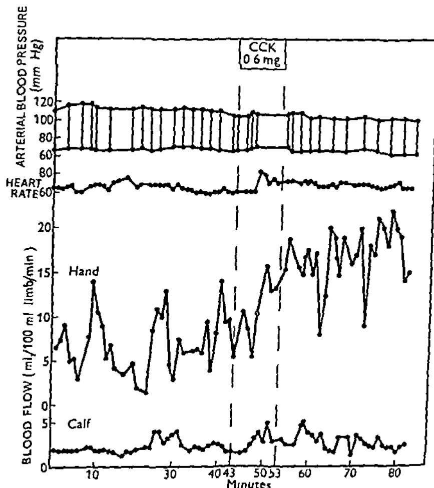


Fig 10 1 Results showing that alkaloids of the ergotoxine group cause vasodilatation in the hand

In this experiment Hydergine (CCK) was administered intravenously It is a mixture of equal parts of dihydroergocornine (DHO) dihydroergocristine and dihydroergocryptine (Barcroft Konzett and Swan 19[illegible]1)

transmitter of sympathetic nerves in normal limbs might not cause vasodilatation in sympathectomized vessels In such limbs vascular tone may not be due to the action of adrenaline but to that of some quite different mechanism (Chapter 7)

Vasodilatation in the hand due to pharmacological agents can result from inhibition of constrictor tone at a number of

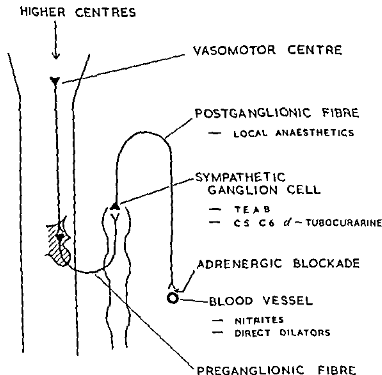


Fig 10 Diagram showing sites of inhibitory action of drugs on sympathetic vasoconstrictor tone

points along the sympathetic efferent pathway or from a direct effect on the blood vessels This is shown diagrammatically in Fig 10 2 We do not need to consider activity of dilator nerves—because these do not exist in the hand (Arnott and Macfie 1948)

Firstly an attempt was made to see if the dihydro alkaloids had a peripheral action This was done by recording the blood flow in both hands and then infusing the alkaloid directly into

the brachial artery on one side Fig 10 3a shows that the intra arterial infusion of 0 2 mg dihydroergocornine caused an increase in blood flow in the ipsilateral but not in the contra lateral hand A similar response was obtained in ten other subjects This indicates that the dihydro alkaloids either

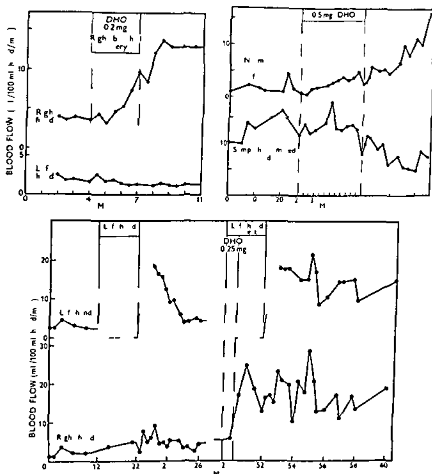


Fig 10 3 Results described fully in the text revealing two distinct vasodilator actions of the alkaloids of the ergotoxine group on the blood vessels *of the hand*
(1) Low concentrations as have to be used in intravenous experiment to avoid toxic effects have little of the peripheral blocking action and release sympathetic tone by a powerful central inhibitory action
(2) High concentration as can be used in intra arterial experiments exert a true local adrenergic blocking action and release sympathetic vaso constrictor tone peripherally (Barcroft Konzett and Swan 1951)

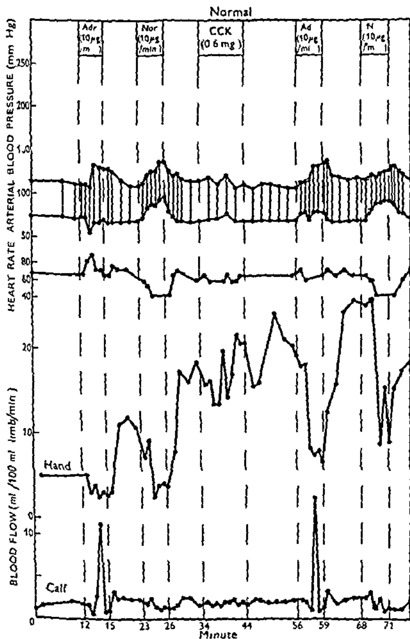
block the tonic constrictor impulses arriving by way of the sympathetic nerves—or otherwise cause a vasodilatation by their direct action on the walls of the blood vessels. To decide between these two possibilities we investigated the action of the dihydro alkaloids on sympathectomized limbs, for if dilatation occurred in the sympathectomized limb one could conclude that the alkaloids caused a relaxation of the blood vessels. This was not found to be the case. While there was no significant change on intravenous administration of the alkaloids in four subjects (Fig. 10.3b), intra-arterial infusions actually caused a vasoconstriction in two subjects. Therefore the vasodilatation seen on intra-arterial infusion of the dihydro alkaloids in normal limbs was due to blocking of the tonic constrictor impulses mediated by the sympathetic nerves—true adrenergic blockade.

It does not necessarily follow, however, that the vasodilatation seen after intravenous infusions in normal subjects is due to the same mechanism. Although the dihydro compounds are less toxic than the natural alkaloids of ergotoxine they still retain certain unpleasant side effects which limit the dose which can be given. Barcroft et al. were unable to give very large doses of the dihydro compounds intravenously, and clearly the amounts given intra-arterially are much larger than the amount reaching the hand following intravenous administration. The following experiment was therefore devised to see whether central inhibition of vasoconstrictor tone—as suggested by Goetz—was responsible for the peripheral dilatation after intravenous administration (Fig. 10.3c).

The resting blood flow was determined in both hands of a normal subject. Then the flow in the left hand was occluded by a cuff for 10 minutes, after which the resultant period of reactive hyperaemia was recorded. After a suitable period of rest the circulation in the left hand was again occluded for 10 minutes, but during the first 3 minutes of this period dihydroergocornine was given intravenously. The blood flow in the unoccluded right hand increased in the usual manner. Now the dihydroergocornine reached the adrenergic nerve endings in the right hand but not in the left hand. Pothlin (1947) had observed that in the rabbit 99 per cent of the dihydro alkaloids were removed from the circulation in 5 minutes. We

considered that little if any dihydroergocornine would remain in the blood when the circulation in the hand was released On release of the occlusion on the left hand the peak of reactive hyperaemia passed off but the blood flow did not return to its previous value—there was a persistent vasodilatation of almost the same degree as in the right hand This must have been due to inhibition of sympathetic vasoconstrictor tone centrally The question arises as to whether inhibition could have been caused in the sympathetic ganglia This appears to be unlikely for Konzett and Rothlin (1950) found no such action on the perfused superior cervical ganglion of the cat Also the occurrence of nausea and vomiting as side effects of the dihydro substances suggest a medullary action Therefore we conclude that the hydrogenated alkaloids of the ergotoxine group have an adrenergic blocking action in man when given in relatively large doses by the intra arterial route When given intravenously however the adrenergic blocking effect is small and the vasodilatation is in the main due to central inhibition of sympathetic vasoconstrictor tone as suggested by Goetz (1949)

Barcroft et al (1951) then investigated the effects of the alkaloids on the response to infusions of adrenaline and noradrenaline for substances which block sympathetic nerve endings are said to be more effective against circulating sympathomimetics Fig 10 4 shows an experiment in which short infusions of adrenaline and noradrenaline were given before and after the intravenous administration of Hydergine It indicates that the dihydro alkaloids had very little effect on the arterial blood pressure or heart rate response to adrenaline or noradrenaline The constrictor action of adrenaline on the skin vessels and of noradrenaline on the skin and muscle vessels was not affected From this and five other similar experiments Barcroft et al concluded that the dihydro compounds had no blocking action on the effects of adrenaline and noradrenaline In this respect their results differed from those of Goetz and Katz (1949) who described reversal of the adrenaline pressor effect after intravenous dihydroergocornine and from those of Kappert (1949) who concluded that dihydroergocornine reversed the constrictor action of adrenaline on the skin vessels We are unable to account for these differences



F g 10 4 Results h w g t] at a larg ıtra nous l se of hy lrog nated alkalo) of the erg tox ne group (Hy lerg n) almost enough to cause toxı ymptoms f l to l lo k the vas) on trictor act on of a l nal ne an l nor adrenal ne ın th hand (Ba roft Konzett and Swan 19ə1)

Adrenaline and noradrenaline given intravenously act upon organs and structures which are almost unaffected by the direct action of the intravenous dose of the dihydro alkaloids It is therefore difficult to see how a strong anti adrenaline effect should have been obtained from doses of alkaloid which when given intravenously act in the main centrally

Regarding the effect of the dihydro alkaloids on the pressor response to adrenaline Goetz and Katz (1949) reported that adrenaline caused a fall in blood pressure when given after dihydroergocornine But Barcroft et al (1951) were unable to confirm this An explanation of this divergence of response might be that while in Barcroft et al s experiments the subject lay supine with one pillow under the head the other investigators may have placed their subjects in a more upright position If the posture is altered fundamental cardiovascular *dynamics are affected and differing results may be obtained* This is all the more true when vasodilator substances have been given and may be responsible for the fact that Barcroft et al found that the dihydro alkaloids failed to lower the blood pressure in normal subjects although a hypotension was reported by several other workers

Barcroft et al also investigated the effects of Hydergine given intra arterially on the constrictor response in the foot to adrenaline and noradrenaline The observations made did not indicate any blocking effect to adrenaline or noradrenaline but they thought that the doses of sympathomimetics used might have exceeded the normal physiological range for man Swan (1951a) studied this aspect of the problem in more detail using *the hand for his investigations Definite constriction occurred in most subjects at a dose rate of* $\frac{1}{8}$ μg adrenaline or noradrenaline per minute when given into the brachial artery Constriction in the hand was also recorded on immersing one foot in water at 12 C The cold constrictor response so obtained is mediated by the sympathetic pathway and is a convenient way of testing sympathetic constrictor tone Then dihydroergocornine 0 1 to 0 25 mg was given intra arterially and the ensuing response to intra arterial adrenaline or noradrenaline or to the cold constrictor test was observed Fig 10 5 is an example in which the constrictor effect of noradrenaline and of the cold stimulus are compared before and

after the dihydro alkaloid It will be seen that the constrictor response to ⅛ μg noradrenaline and to cold were abolished by the dihydro alkaloids and the response to ¼ μg noradrenaline is very slightly reduced The same observations were also made with respect to adrenaline The blockade so produced can be overcome by larger doses of adrenaline or noradrenaline

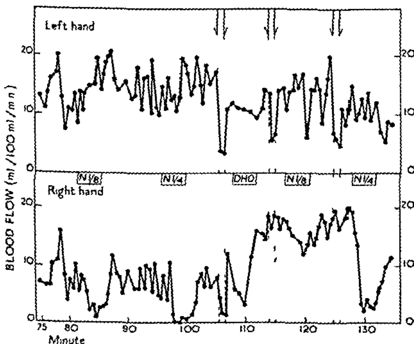


Fig 10 5 Given intra arterially reaching the right hand in high concentration dihydroergocornine (DHO) blocked the peripheral vasoconstrictor action of a small dose of noradrenaline (N ⅛) and also that induced reflexly by placing the feet in cold water (between pairs of vertical broken lines)

it has been present up to 30 min after the dihydro alkaloids were given The effect of the dihydro alkaloids on the adrenaline and noradrenaline effect on the muscle blood vessels is variable—but in general the response is unchanged

We are not in this work concerned with the overall effects of the dihydro alkaloids on the circulation An adrenergic blocking action has been conclusively demonstrated—but as we have already pointed out the effects observed must be

critically interpreted The responses in the intact organism are complex representing the sum of local and general effects At times the local effect may be marked Grayson and Swan (1950) found that local injection of the dihydro alkaloids into human colonic mucosa exposed at colostomy caused a vaso dilatation Yet when the alkaloids were given intravenously a vasoconstriction occurred in the colonic mucosa

To summarize the position in regard to the effects of the hydrogenated alkaloids in the human peripheral circulation we may say that although in large amounts they produce true adrenergic blockade toxic effects permit the general adminis tration of doses which only cause vasodilatation by a central inhibition of sympathetic vasoconstrictor tone

2 *The Benzodioxanes*

Although these blocking agents have a relatively weak action in comparison to others one of their number is of considerable interest in man—because it is used in the diagnosis of phaeo chromocytoma of the adrenal gland The several members of this series fall into two different types and are designated by a numeral followed by the letter F (Fourneau—who synthesized the series) Those substances which are more effective against the effect of sympathetic stimulation than against circulating adrenaline and noradrenaline are typified by the compound 833F while those which are more effective against circulating adrenal hormones are represented by the compound 933F The adrenergic blockade produced by the benzodioxanes in animals is weak when compared to other substances There are many aspects of sympathetic and humoral action which are not affected by them Finally these compounds are the only adrenergic blocking agents which accelerate the inactivation of adrenaline (Morrison and Lissak 1938)

In 1947 Goldenberg Snyder and Aranow described the benzodioxane test for phaeochromocytoma In this test 0 25 mg 933F per kilogram body weight is injected intraven ously If the arterial blood pressure is elevated due to the presence of circulating pressor hormones then a fall in blood pressure of 10–15 min duration is observed but if the case is one of essential or renal hypertension then the blood pressure usually rises slightly This test is now of proven value in the diagnosis of phaeochromocytoma In their original

paper Goldenberg et al (1947) reported an investigation in which continuous infusions of adrenaline were given to normal subjects When the blood pressure was stable 933F was injected intravenously producing a fall in blood pressure

From Goldenberg's experimental results it would appear that 933F was either blocking the augmentor effect of adrenaline on the cardiac output or was lowering further the already diminished total peripheral resistance From animal experiments the former possibility appeared unlikely (de Vleeschhouwer 1947) It occurred to Prunty and Swan that plethysmographic determination of limb blood flow might assist in the interpretation of the action of 933F on the overall peripheral resistance The latter workers also investigated the effect of 933F on the hypertension produced by infusions of noradrenaline in normal subjects

Prunty and Swan (1950) measured calf and hand blood flow in normal subjects lying supine with the head elevated 15 to the horizontal The blood pressure was measured with the sphygmomanometer Continuous infusions of adrenaline or noradrenaline were given and the vascular response recorded for about 20 minutes by which time the circulatory changes had stabilized Then a dose of 0 1 mg 933F per kilogram body weight was slowly injected either directly into the tube through which the adrenaline or noradrenaline infusion was being maintained or in some subjects was injected into another suitable vein The ensuing responses were noted the infusion of adrenaline or noradrenaline being maintained

An experiment in which a continuous adrenaline infusion was given is shown in Fig 10 6 The adrenaline infusion increased the systolic blood pressure while the diastolic pressure declined The calf blood flow is increased At the arrow 15 mg 933F was injected over about 90 sec This resulted in a brisk increase in heart rate and an intense flushing of the face and neck There was a further increase in calf blood flow The diastolic blood pressure fell further but recovered to its previous value within a few minutes The systolic pressure also declined slightly but then rose to a maximum value of 185 mm Hg There was a moderate but gradual fall in blood pressure for the remainder of the adrenaline infusion This subject did not complain of symptoms other than palpitation Most subjects

however experienced a metallic taste in the mouth—with severe palpitations a burning sensation in the face and neck pulsations in various parts of the body and a sense of alarm One subject (No 6) experienced symptoms suggestive of an

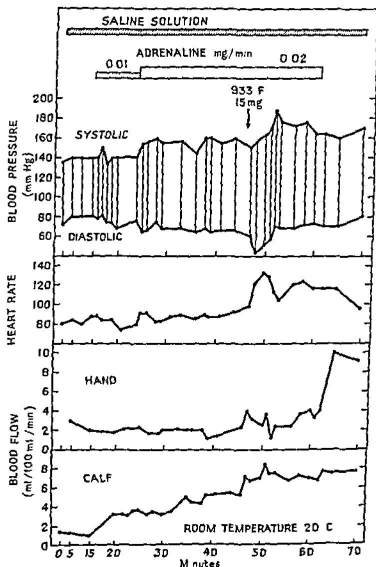


Fig 10 6 Result showing failure of benzodioxane (933F) to block the hypertensive action of adrenaline (Prunty and Swan 19[illegible]0)

TABLE IX

Blood pressure and heart rate

Subject No	Age Yrs	Drug		Basal	3 min before 933F	1 min after 933F	3 min after 933F	10 min after 933F
1	45	Adr	BP Pulse	130 [illegible] 88	1[illegible]2/74 110	138/[illegible] 1[illegible]2	160/76 13[illegible]	168/80 1[illegible]0
2	[illegible]3	Adr	BP Pulse	130 80 80	158/72 90	158/40 120	170/[illegible]5 1[illegible]8	175/68 1[illegible]0
3	[illegible]	Adr	BP Pulse	125 80 80	15[illegible]/56 88	145/4[illegible] 104	158 65 112	17[illegible] [illegible]8 104
4	23	Adr	BP Pulse	140 80 [illegible]6	15[illegible]/6[illegible] 72	1[illegible] 40 112	190 60 100	17[illegible] [illegible]8 104
5	8	Adr	BP Pulse	118 [illegible]0 66	1[illegible]0/66 90	174/[illegible]0 138	174 [illegible]0 114	1[illegible]6 [illegible]6 108
6	23	Nor	BP Pulse	1[illegible] 7[illegible] [illegible]	145/106 64	14[illegible] 98 96	14[illegible] 108 68	1[illegible]0 108 66
7	7	Nor	BP Pulse	13[illegible] [illegible] 8[illegible]	184/104 68	[illegible]00 7[illegible] 140	190/80 108	180 9[illegible] 9[illegible]
8	3[illegible]	Nor	BP Pulse	1[illegible]0 80 [illegible]8	156/105 [illegible]6	1[illegible]0 [illegible]0 [illegible]6	170 90 104	165/85 78
9	9	Nor	BP Pulse	130 [illegible]5 [illegible]0	170/100 36	168 68 45	160 5[illegible] [illegible]4	170 75 48

encephalopathy Table IX shows the response of blood pressure and heart rate in nine normal subjects of whom five received adrenaline and four noradrenaline It was thought that apart from subject No 9 no significant fall in blood pressure had been demonstrated In the peripheral circulation an increase in blood flow occurred after the injection of 933F in both hand and calf

The results reported above were at variance with those of

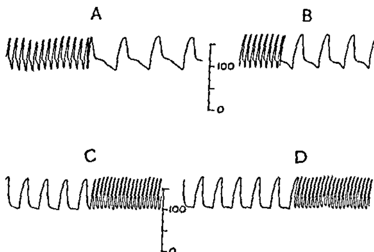


Fig 10 7 Records showing that benzodioxane (933F) probably increases cardiac output

Intra arterial tracings of the blood pressure in the brachial artery during the continuous intravenous infusion of adrenaline at the rate of 10 µg min *A B* before *C D* after intravenous injection of 15 mg benzodioxane (933F) After the 933F the pressure falls more rapidly during diastole and the heart rate is increased This implies a decrease in total peripheral resistance and an increase in cardiac output

Goldenberg et al (1947) and Goldenberg and Aranow (1950) insofar as Prunty and Swan did not consider the responses they obtained could be regarded as depressor How can this difference be explained ? Firstly it must be remembered that the blood pressure is a balance between the cardiac output and the total peripheral resistance *Although Prunty and Swan* did not measure the cardiac output they thought that it was increased Pulse contour tracings obtained with a sensitive capacitance manometer (Fig 10 7) supported this The increased cardiac output was considered to overcompensate for

the undoubted peripheral vasodilatation and so a rise in systemic arterial pressure soon occurred Now posture may play a considerable part in determining vascular responses because it will affect the distribution of blood in the veins the right auricular pressure and other variables It is possible that this factor is at least in part responsible for the different results obtained by Prunty and Swan and also by Freis et al (1951) It is difficult however to describe the short hypotension produced by 933F as evidence of adrenergic blockade

Using the intra arterial infusion techniques Swan (1951b) investigated the effect of 933F on the blood flow in the hand and also on its effect on adrenaline and noradrenaline vaso constriction Briefly—2 mg 933F given intra arterially caused a moderate increase in blood flow of 5–11 minutes duration in six normal subjects But almost the same vasodilatation was observed in two sympathectomized limbs when 933F was given intra arterially This suggested that 933F in these doses has in part at least a direct dilator effect on blood vessels Further experiments are needed to prove this point

If an injection of 1–2 mg 933F was made during an infusion of adrenaline or noradrenaline in intra brachial doses up to 0 , μg per minute a transient abolition of the vasoconstriction was seen The constrictor effect of infusions of $\frac{1}{8}$ μg per minute adrenaline or noradrenaline was reduced by the prior injection of 1–2 mg 933F Small doses of 933F (0 1 mg to 0 5 mg) had little effect on the adrenaline or noradrenaline vasoconstriction although they did cause some increase in blood flow

These results at present incomplete indicate that 933F in large doses has a weak adrenergic blocking action in man They do not however explain the action on the arterial blood pressure described by Goldenberg et al (1947) and Goldenberg and Aranow (1950)

3 *Priscol*

This substance is an effective vasodilator in doses which may be given to the human subject The side effects with large doses include tachycardia flushing and conjunctival injection We have had little experience of its use in this laboratory but our findings agree in general with those of Wakim et al (1950)

Our observations are reported only to indicate future problems to be dealt with

We have seen vasodilatation in effectively sympathectomized limbs thus confirming Grimson et al (1948) In addition we have investigated the effects of intravenous infusions of adrenaline and noradrenaline on the peripheral blood flow finding that the constrictor effect in the skin (and in the case of noradrenaline in muscle) is much reduced after 50 mg priscol given intravenously The blood pressure response to the circulating sympathomimetics is unchanged

4 *Dibenamine*

This substance is probably the most effective adrenergic blocking agent available (Nickerson and Goodman 1947) It has not been the subject of extensive investigation in man apart from that reported by Hecht and Anderson (1947) These workers reported that dibenamine inhibited the pressor effects of adrenaline and the pressor response to cold One of the difficulties in the study of the effect of dibenamine in normal subjects is the duration of its action Orthostatic hypotension may last for hours after effective doses of dibenamine The use of intra arterial technique should overcome this obstacle to experimental investigation

Summary

Adrenergic blocking agents are those substances which specifically inhibit the response of the effector cell to the sympathetic transmitter and to circulating sympathomimetic agents All the groups of substances which produce adrenergic blockade in animals can be shown to do so in man also However the dose required to be effective by the intravenous route is frequently not tolerated because of unpleasant side effects so that only in the case of dibenamine and perhaps priscol has true adrenergic blockade been demonstrated on intravenous administration The hydrogenated ergotoxine alkaloids and 933F have a blocking action when given in relatively large doses intra arterially

REFERENCES

Arnott W M and Macfie J M (1948) *J Physiol* 107 233
Barcroft H Konzett H and Swan H J C (1951) *J Physiol* 112 273

Bluntschli H J and Goetz R H (1947) *S Afr med J* **21** 382
Dale H H (1906) *J Physiol* **34** 163
Freis F D Stanton J R and Wilkins R W (1948) *Amer J med Sci* **216** 163
Freis F D Mackay J C and Oliver W F (1951) *Circulation* **3** 254
Goetz R H (1949) *Lancet* **1** 510
Goetz R H and Katz A (1949) *Lancet* **1** 560
Goldenberg M Snyder C H and Aranow H (1947) *J Amer med Ass* **135** 971
Goldenberg M and Aranow H (1950) *J Amer med Ass* **143** 1139
Grayson J and Swan H J C (1950) *Lancet* **1** 488
Grimson K S Reardon M J Marzoni F A and Hendrix J P (1948) *Ann Surg* **127** 968
Hayes D W Wakim K G Horton B T and Peters G A (1949) *J clin Invest* **28** 615
Hecht H H and Anderson R B (1947) *Amer J Med* **3** 3
Kappert A (1949) *Helv med Acta Sup* **22** 27
Konzett H and Rothlin E (1950) Unpublished observations
Morrison R S and Lissak K (1938) *Amer J Physiol* **123** 404
Nickerson M (1949) *J Pharm pharm Rev* **1** 27
Nickerson M and Goodman L S (1947) *J Pharmacol* **89** 167
Frunty F T G and Swan H J C (1950) *Lancet* **1** 759
Rothlin E (1947) *Bull schweiz Akad med Wiss* **2** 249
Stoll A and Hofmann A (1943a) *Helv chim Acta* **26** 1570
—— (1943b) *Helv chim Acta* **26** 2070
Swan H J C (1951a) Unpublished results
—— (1951b) Unpublished results
—— (1951c) *Brit med J* **1** 440
Vleeschhouwer G R de (1947) *Proc Soc exp Biol N Y* **66** 151
Wakim K G Peters G A and Horton B T (1950) *J Lab clin Med* **35** 50

CHAPTER 11

PHAEOCHROME TUMOURS

Recent advances in our knowledge concerning the nature of the transmitter agents of the sympathoadrenal system has led to better understanding of the effects of these substances in man A condition which gives rise to an excessive liberation is a secreting tumour of the adrenal medullary tissue The majority of such tumours lie in or near the suprarenal glands but also arise in para aortic rests of medullary tissue The tumours are usually benign adenomata but about 10 per cent are malignant They are known as phaeochromocytomata and are commonly unilateral in 12–15 per cent of cases more than one tumour is present

Until recently phaeochromocytoma was thought to be a rare condition but it is now clear that if the possibility of medullary tumour is considered in certain hypertensive patients unsus pected cases may be diagnosed In all 270 cases had been reported up to 1949 of which 67 per cent were proven post mortem (Smithwick et al 1950) Early diagnosis and surgical removal frequently results in complete recovery of normal health Therapeutic advances now permit more accurate *diagnosis of the condition and have reduced the operative* mortality thus a more favourable prognosis may be given We will therefore consider the clinical aspects of the condition and discuss this sole example of disordered physiology of adrenal medullary function

A reasonable concept of the role of adrenaline and nor adrenaline in the body would be to ascribe the sympathetic transmission to the latter and emergency adrenal medullary function to the former It is probable that the adrenal medulla discharges an effective amount of adrenaline into the circulation during stress Although the natural secretion of the adrenal gland contains up to 70 per cent noradrenaline the mixture will have the effect of adrenaline (de Largy et al 1950) But in phaeochromocytoma this function is disordered Firstly large amounts of the medullary hormone are released into the

circulation The quantities liberated are far in excess of the need during emergency and cause responses which are harmful Also the predominant hormone liberated from phaeochromo cytoma is not always adrenaline for excess of noradrenaline may be found Noradrenaline does not further the response to emergency—indeed its actions antagonize adrenaline in many respects Finally in a large number of cases there is evidence of a liberation of excessive amounts of medullary hormone over a long period of time which is in contrast to the intermittent response to stress

The majority of patients suffering from phaeochromocytoma present symptoms referable to their hypertension but some times metabolic symptoms predominate A tentative classi fication is as follows

(*A*) *Hypertensive Group*

1 Paroxysmal hypertension —sympathico adrenal syndrome
2 Elevated resting blood pressure—paroxysmal hyper tension superimposed
3 Sustained hypertension in many aspects similar to essen tial or malignant hypertension but certain metabolic signs are present
4 Sustained hypertension identical with essential hyper tension

(*B*) *Metabolic Group*

5 Glycosuria elevated metabolic rate and sustained hyper tension
6 Metabolic symptoms episodes of paroxysmal hyperten sion

1 Paroxysmal hypertension This syndrome is charac terized by sudden attacks consisting of palpitation nausea and sometimes vomiting headache substernal pain pallor of the face and extremities and tremor (Mackeith 1944) At times fear out of proportion to the severity of the attack occurs

The symptoms may be quite mild or of great severity—indeed the patient may die during or after an attack The duration of the attack is commonly about one hour—but fre quently attacks last only a few minutes They may recur daily or only at intervals of months and may alter in severity If the patient is seen during an attack pallor of the face and

extremities will be noted while the general condition will vary with the severity of the attack The systolic blood pressure is sometimes 300 mm Hg and there is also a diastolic hyper tension The blood pressure frequently varies during the attack The radial pulse is usually hard the rate varies from patient to patient In several patients extreme bradycardia has been noticed during the attack The extremities are cold and blanched but usually moist Sweating is common during the attacks at times streams of sweat course down the patient s face and trunk while the hands and feet are relatively dry The mouth temperature is usually elevated during a paroxysmal attack Urinary examination frequently reveals glycosuria The paroxysm may terminate fatally by reason of acute pulmonary oedema or cerebral haemorrhage Other wise the patient suddenly becomes aware that his unpleasant symptoms are diminishing Sweating may persist and indeed increase while flushing of the face and extremities is common The flushing may be associated with a sensation of warmth spreading over the neck and face The blood pressure falls rapidly to normal or subnormal values In some cases this fall may be extreme and ultimately fatal For a more complete account see Mackeith (1944)

2 A number of patients have been seen in whom the resting blood pressure level is high and who suffer from further paroxysms of hypertension superimposed upon a symptomless hypertensive state They may represent an intermediate group between 1 and 3 and are separated here from the other groups because they represent a different diagnostic problem

3 Patients with sustained hypertension closely resembling essential hypertension and without evident paroxysms of hypertension This group probably contains the greatest number of patients suffering from phaeochromocytoma Green (1946) reviewed 51 adequately reported cases which he selected from the literature and observed that 70 per cent had suffered from sustained hypertension during life

The patients may have mild or severe hypertensive symptoms or may at times exhibit signs consistent with malignant hypertension The differentiation of the rare phaeochromocytoma from the common essential hypertension is therefore a problem to test the diagnostic skill of the

physician In the majority of these cases however symptoms and signs are present which may suggest the correct diagnosis The most important of these is excessive sweating Smithwick et al (1950) reported that this symptom occurred in only 2 per cent of patients with essential hypertension but in 9 out of 10 patients with phaeochromocytoma Symptoms referable to a vasospastic condition of the hands and a raised mouth temperature were also reported by many patients with phaeochromocytoma—but were uncommon in essential hypertension A raised basal metabolic rate glycosuria and an elevated fasting blood sugar also occur more frequently than in essential hypertension

4 Patients with sustained hypertension without any symptoms suggestive of adrenal medullary dysfunction This variety is uncommon and usually is drawn from post mortem material Although the symptoms during life may have been inadequately noted in some cases it seems clear that some patients with a medullary tumour die in cardiac failure without any symptoms referable to the tumour

5 Glycosuria elevated metabolic rate and sustained hypertension In some patients the metabolic symptoms may predominate and when weight loss is extreme an endocrine disturbance is suggested When a high fasting blood sugar is discovered diabetes mellitus may be considered A good example of this variety is the case reported by Raab and Smithwick (1949)

6 In a small minority of patients metabolic symptoms and signs predominate while the blood pressure remains normal Paroxysmal hypertension only occurs These patients are usually considered to have other endocrine disorders

ADRENALINE NORADRENALINE AND PHAEOCHROMOCYTOMA

It is certain that both adrenaline and noradrenaline are present in excess in the blood of patients suffering from phaeochromocytoma Holton (1948) and Goldenberg et al (1949) have reported large quantities of both amines in tumours following surgical removal while Engel and Euler (1950) have demonstrated large quantities of adrenaline and noradrenaline in the urine of such patients We discussed in earlier chapters information obtained from infusions of adrenaline and

noradrenaline in normal subjects Are the symptoms and signs in patients similar to the laboratory findings on infusion of the amines in normals? In certain important respects this is not so The probable explanation of the discrepancy lies in the differing rates in which the hormones enter the circulation In phaeochromocytoma enormous quantities are liberated and effects are therefore seen which could not be deliberately induced in normal subjects nor indeed tolerated by them

We will therefore discuss the signs and symptoms of phaeochromocytoma in regard to the known action of adrenaline and noradrenaline in man and consider the discrepancies which exist

Both adrenaline and noradrenaline cause the normal subject mental disturbance adrenaline to a greater extent than noradrenaline This varies from subject to subject—but on two occasions subjects who had previously had adrenaline reported their sense of alarm to be much greater with noradrenaline Palpitation and tachycardia as caused by adrenaline or bradycardia (Barnett et al 1950 case 3) as with noradrenaline have been reported in patients The tremor weakness and fatigue common in patients are all seen on infusion of adrenaline in normal subjects A symptom of interest is the excessive sweating which is a feature of phaeochromocytoma We have never seen sweating in some 300 infusions in normal subjects The sweating in phaeochromocytoma has been attributed to a retention of heat owing to the cutaneous vasoconstriction But there are reasons for believing that this may not always be so Many cases have been reported in which profuse sweating occurred within a few seconds of the appearance of pallor and frequently in association with headache Also it is strange that we have never seen sweating in normals in spite of long *infusions which caused sustained pallor and presumably* considerable heat retention It seems likely that hypothalamic stimulation may be responsible for this symptom Swan (1951a) observed that sweating persisted for a week after removal of a tumour

Flushing and vasomotor collapse have been reported following hormonal discharge The flushing is probably similar to that seen following the end of an adrenaline infusion Smithwick et al (1950) also thought that a heat retention mechanism

might underlie this response But adrenaline causes a central inhibition of vasoconstrictor tone (Swan 1951b) This is not thought to be due to heat retention for although vasodilatation in the hand was found to follow 20 μg adrenaline for 3 min it occurred only infrequently after 10 μg for 10 min

A more extreme response probably of the same nature is the hypotension observed after doses of 100 μg per minute (Green et al 1948) Collapse is not infrequently seen both during the course of the disease or after removal of the tumour at operation This collapse may be transient due to inhibition of vasomotor tone and will respond well to intravenous nor adrenaline But at times an irreversible effect is produced Hypotension anuria and death may result in spite of heroic efforts at medication This latter state corresponds to the adrenaline shock seen in animals after massive doses of adrenaline (Vigran and Essex 1949)

The changes in blood pressure and overall haemodynamics are of considerable interest Briefly both adrenaline and nor adrenaline increase the systolic blood pressure in normal subjects but whereas noradrenaline also elevates the diastolic pressure adrenaline usually causes no change or a slight fall in the diastolic pressure We have seen a rise in diastolic pressure only occasionally with moderate doses of adrenaline in normals Goldenberg et al (1948) observed that while noradrenaline increased the total peripheral resistance moderate doses of adrenaline caused an overall vasodilatation Now patients with phaeochromocytoma have always a high diastolic pressure if they are in a hypertensive state and the superficial evidence pointed to a raised total peripheral resistance This suggested to Prunty and Swan (1950) that it was likely that noradrenaline and not adrenaline caused the hypertension But it is now clear that this is not the case for tumours containing predominantly adrenaline have been removed from patients who had considerable elevation of the diastolic pressure Whereas small doses of adrenaline cause an overall vasodilatation larger amounts such as occur in phaeochromocytoma must cause an overall increase in peripheral resistance (Goldenberg et al 1950) a concept of adrenaline action in keeping with observations made in the dog and cat There is some direct evidence for this action in man Whereas small doses

of adrenaline given intra arterially cause little change in the calf blood flow doses greater than 6 μg per minute cause a definite reduction in blood flow (Swan 1951) Therefore it is clear that both amines can cause a rise in diastolic blood pressure and an overall vasoconstriction

Increased oxygen consumption and an elevation of the blood sugar have been reported to follow adrenaline infusion With noradrenaline the metabolic effects are much less Reale et al (1950) found no alteration in the oxygen consumption during infusions of noradrenaline in normals This might lead one to suppose that patients who exhibited metabolic symptoms might have tumours containing predominantly adrenaline But this is not the case for high fasting blood sugar levels and raised metabolic rate have been observed in patients with 88 per cent and 97 per cent noradrenaline tumour contents (Goldenberg et al 1950 cases 13 and 12) We must therefore conclude that at high dose levels noradrenaline *influences* metabolism by either a direct or indirect action

This discussion has so far centred around the production of the main symptoms and signs in phaeochromocytoma by the action of adrenaline and noradrenaline We will now concern ourselves with the clinical classification of the condition as suggested in the beginning of this chapter We divided the condition into those presenting with predominantly hyper tensive symptoms and signs and those with hypermetabolic manifestations

The former group shows the development of a definite pattern of hypertension Thus some patients exhibit paroxysmal hypertension (Group I) others have an elevated basic pressure on which an additional paroxysmal hypertension is clearly superimposed (Group II) The majority of patients have clear evidence of sustained hypertension with indefinite evidence of further paroxysms of hypertension (Group III) and finally a minority of patients die from a hypertension in no way different from essential hypertension (Group IV)

Let us suppose that in the natural history of an adrenal medullary tumour the discharge of hormone is at first par oxysmal but after some time a small continuous basal libera tion is established with superimposed paroxysmal discharge occurring from time to time Gradually the basal secretion

might increase with a progressive diminution of the effects of paroxysmal hormonal discharge This is a reasonable view to take as the level to which the blood pressure can rise with survival of the patient is reduced with the progressive elevation of the basal blood pressure and paroxysms of great intensity are not likely to be frequent Finally it is possible that a state may be reached in which further production of medullary

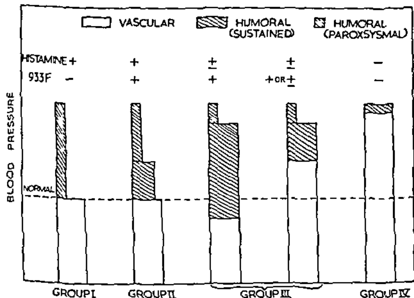


Fig 11 1 Classification of phaeochrome tumours according to the relative amounts of humoral paroxysmal humoral sustained and essential (vascular sustained) hypertensive element

The relative importance of the paroxysmal element may be judged by the extent of the blood pressure rise caused by histamine The relative importance of the sustained hypertensive element may be judged by the extent to which the blood pressure is lowered by 933F

hormone is no longer necessary to maintain hypertension and another mechanism has developed in response to the continued release of the amines Or perhaps this group represents the normal occurrence of essential hypertension in a group of individuals Fig 11 1 diagrammatically represents the present concept The disease may be present in any stage and remain there or progress to another variety It is clear that many tumours are present for a considerable time for calcification

in degenerated areas in the tumour have been reported It would therefore seem reasonable to take the view that the patient's symptoms might change as the secretory activity of the tumour altered It would also seem reasonable to associate a sustained hypertension to a continuous release of adrenaline and noradrenaline although it is possible that other activities stimulated by transient discharge of medullary hormone for example pituitary ACTH might cause the sustained hyper tension This possibility is supported by the occasional finding of a slow fall in blood pressure lasting several days after removal of the tumour

In the metabolic group less information of day to day changes is available but it seems clear that a mechanism exists in which transient hormone liberation results in sustained endocrine changes Further speculation on this aspect is not warranted in our present state of knowledge

The Diagnosis of Phaeochromocytoma

The ultimate diagnosis of the condition depends either upon the anatomical localization of its presence or on the demon stration of circulating adrenaline and noradrenaline The dis cussion of the anatomical localization is not our purpose here suffice to say that in the case of small tumours it is difficult if not impossible and that a number of unsuspected tumours have been discovered at operation or post mortem The demonstration of excess medullary hormone may be achieved either directly in blood or urine or by producing effects which only occur in association with a biologically active tumour The demonstration of an excess of adrenaline or noradrenaline in blood is not always feasible but the amounts excreted in the urine can be estimated (Engel and Euler 1950) These workers demonstrated a great increase in the urine content of adrenaline and noradrenaline in two patients with phaeo chromocytoma and also found a good correlation between the relative preponderance of either amine in the urine with the concentration in the tumour

The pharmacological tests which seek to demonstrate specific effects due to circulating medullary hormones are more complex The first group are those which produce a paroxysmal discharge of medullary hormone of which the best

known is the histamine test of Roth and Kvale (1945) An intravenous injection of 0.5 mg histamine is given to the patient If a phaeochromocytoma is present there is a brisk rise in blood pressure often to extreme limits with associate symptoms similar to those experienced during the paroxysmal attacks It is clear that this test will be of greatest use in the patients in Group I and the accuracy will decrease in Group III Indeed a moderate rise of blood pressure sometimes follows an intravenous histamine in essential hypertension and therefore the interpretation of this test may be difficult A positive response to the histamine test is a rise in blood pressure greater than the response to the cold pressor test Histamine probably acts by a direct stimulation of the cells of the adrenal medulla and not by a reflex In normals only small amounts of hormone are liberated insufficient to cause much effect but with phaeochromocytoma large amounts enter the circulation A number of other substances also cause transient liberation of pressor hormones from the adrenals These are adequately considered in the clinical literature

The second group of pharmacological substances are those which modify the action of adrenaline or noradrenaline Of these the most important is 933F (piperidyl methylbenzodioxane) In 1947 Goldenberg Snyder and Aranow demonstrated a fall in blood pressure in patients with phaeochromocytoma following injection of 0 25 mg 933F per kilogram body weight In patients with essential hypertension this amount of adrenergic blocking agent caused either no change or a rise in blood pressure Goldenberg and Aranow (1950) were able to report 59 positive (vaso depressor) no false positive and 3 false negative responses to this test Clearly on clinical grounds the 933F test is of value in the diagnosis of phaeochromocytoma But a negative response will be observed if the test is carried out in patients who are non hypertensive or if the hypertension is due to permanent vascular change

Although of great clinical value the physiological basis of this test is complex and requires further elucidation In an earlier chapter we discussed the observations of Prunty and Swan (1950) who were unable to obtain a fall in blood pressure on injection of 933F in normal subjects rendered hypertensive by means of a continuous infusion of adrenaline We wonder

whether the dose of 933F given to humans by the intravenous route is sufficient to produce true adrenergic blockade. In general the duration of the adrenergic blocking action of 933F is much less than the reported period of hypotension following its administration to patients suffering from phaeochromocytoma.

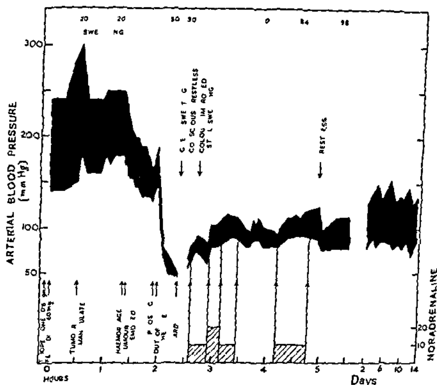


Fig 11 2 The arterial blood pressure during and after the surgical removal of a phaeochromocytoma.
The hatched squares indicate the rate of administration of L noradrenaline intravenously in μg per minute. After [illegible] minutes the infusion of noradrenaline was replaced by one of saline but as the systolic pressure fell below 100 mm Hg the noradrenaline was restarted. After a further infusion of noradrenaline for [illegible] minutes the pressure remained at a satisfactory level (Swan 1951a)

The treatment of this condition is the surgical removal of the tumour. In most cases this is technically easy—but care must be taken to avoid or combat a post operative hypotensive state which frequently develops. Fig 11 2 shows the changes in blood pressure in a 42 year old man during and after surgical

removal of a phaeochromocytoma (Swan 1951a) In this patient an infusion of noradrenaline was used to maintain the blood pressure In this case there had been sustained hyper tension of 10 years standing and the tumour contained more than 90 per cent noradrenaline It was considered that the noradrenaline acted as a temporary replacement of the tumour secretion which had been so acutely removed Not all patients in hypotension respond to medication as favourably as the case just mentioned Indeed several cases have been reported in which the hypotension was unaffected by heroic efforts at medication This is probably due to a condition analogous to the adrenaline shock described by Vigran and Essex (1949) In an attempt to avoid this fatal complication Cahill and Monteith (1951) used dibenamine in two cases before operation with a favourable result

REFERENCES

Barnett A J Blackett R B Depoorter A E Sanderson I H and Wilson C M (1950) *Clin Sci* **9** 151

Cahill C F and Monteith J C (1951) *New Engl J Med* **244** 657

le Largy C Greenfield A D M McCarry R L and Whelan R F (1950) *Clin Sci* **9** 71

Engel A and Euler U S von (1950) *Lancet* **2** 387

Goldenberg M Snyder C H and Aranow H (1947) *J Amer med Ass* **135** 971

Goldenberg M Pines K L Baldwin E de F Greene D G and Roh C E (1948) *Amer J Med* **5** 79

Goldenberg M Faber M Alston E J and Chargaff E C (1949) *Science* **109** 534

Goldenberg M Aranow H Smith A A and Faber M (1950) *Arch intern Med* **86** 823

Goldenberg M and Aranow H (1950) *J Amer med Ass* **143** 1139

Green D M (1946) *J Amer med Ass* **131** 1260

Green D M Johnson A D Lobb A and Cusick G (1948) *J Lab clin Med* **33** 332

Holton P (1949) *J Physiol* **108** 525

Mackeith R (1944) *Brit Heart J* **6** 1

Prunty F T G and Swan H J C (1950) *Lancet* **1** 759

Raab W and Smithwick R H (1949) *J clin Endocrinol* **9** 782

Reale A Kappert A Skoglund C H and Sutton G C (1950) *Acta physiol Scand* **20** 153

Roth G M and Kvale W F (1945) *Amer J med Sci* **210** 653

Smithwick P H Greer W E R Robertson C W and Wilkins R W (1950) *New Engl J Med* **242** 252

Swan H J C (1951a) *Brit med J* **1** 440

—— (1951b) *J Physiol* **112** 426

—— (1951c) Unpublished observations

Vigran I M and Essex H E (1949) *Amer J Physiol* **162** 230

CHAPTER 12

THE VASO VAGAL SYNDROME

It will be remembered that Barcroft Edholm McMichael and Sharpey Schafer showed that the vasomotor centre could excite active vasodilatation in skeletal muscle during fainting (Chapter 2) Other circulatory changes taking place in this curious and common circulatory mishap will be described in this chapter

Michael Foster (1888) believed that fainting was a form of cardiac syncope due to vagal inhibition of the heart The out put arterial blood pressure and cerebral blood flow dwindled and consciousness was lost In World War I Lewis (Cotton and Lewis 1918 Lewis 1932) questioned this In the dog Starling had shown that vagal inhibition comparable with that in fainting did not materially diminish the arterial blood pres sure increase in stroke volume compensated for decreased rate Neither was there hypotension in heartblock though the heart rate was halved Lewis concluded that the fall in blood pressure must be due to peripheral vasodilatation To confirm this he atropinized subjects who had just fainted the brady cardia was abolished but the blood pressure fall persisted He introduced the term vaso vagal syndrome to emphasize that both vagal inhibition and peripheral vasodilatation were among the physiological changes taking place in the faint

Soma Weiss Wilkins and Haynes (1937) and Wilkins Haynes and Weiss (1937) induced faints for the purpose of investigation This they did by oral administration of sodium nitrite followed by tilting upright They confirmed that the fall in blood pressure persisted after atropinization and con cluded likewise that it was due to peripheral vasodilatation Their concept of the nature of the dilatation differed from Lewis s Lewis seems to have considered it as being arteriolar causing decrease in resistance and so fall in pressure They thought it was venous causing decrease in the effective blood volume and so decrease in output During collapse in the upright position they sometimes recorded negative venous

pressures at heart level They thought that the arterioles were constricted since the blood flow in the hand decreased to zero But they observed that the circulation in the legs was not much changed since the oxygen saturation of the femoral venous blood remained normal (their table shows an increase)

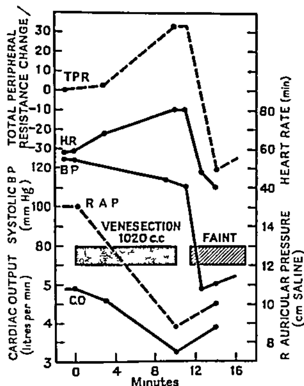


Fig 12 1 Result obtained by McMichael and Sharpey Schafer in an experiment on a Friends Ambulance Unit Volunteer showing that fainting is not a form of cardiac syncope
During the faint in this subject the cardiac output actually increased (Barcroft Edholm McMichael and Sharpey Schafer 1944)

McMichael and Sharpey Schafer (Barcroft Edholm McMichael and Sharpey Schafer 1944) were the first actually to measure the right auricular pressure and cardiac output by cardiac catheterization during the faint Neither changed appreciably as shown in Fig 12 1 Their findings have since been confirmed by Warren Brannon Stead and Merrill (1945)

and by Wood and Burchell (1950) Fainting was not a form of cardiac syncope The abrupt fall in blood pressure was due to decrease in peripheral resistance

In the same investigation at the British Postgraduate Medical School peripheral vasodilatation was found in the skeletal muscles and later shown to be of nervous origin (Chapter 2) In connection with this Sharpey Schafer found an apt observation of John Hunter s (1793) I bled a lady but she fainted and while she continued in the fit the colour of the blood that came from the vein was a fine scarlet Commenting on this before the publication of our results McDowall (1938) thought it signified muscle vasodilatation Increased muscle blood flow during fainting probably also explains the rise in brachial venous pressure previously observed by Ershler Kossman and White (1943)

The question arises as to whether this vasodilatation in muscle also occurs in fainting due to causes other than haemorrhage Is it really part of the vaso vagal syndrome ? Emotional fainting is the commonest manifestation of the syndrome, but here one is up against the difficulty of inducing a subject to faint from emotion while his forearm is in a plethysmograph However during an experiment one of Sharpey Schafer s subjects did faint spontaneously and increase in forearm blood flow was recorded (Brigden Howarth and Sharpey Schafer 1950) This was confirmed by Greenfield (1951) A preclinical student who fainted at the sight of blood offered to act as subject But in the experiment when shown a syringe of blood he did not do so As he and Greenfield were anxious for a faint Greenfield put the blood in a beaker and asked him to drink it This was successful and the fall in blood pressure bradycardia and increase in forearm blood flow seen in Fig 12 2 were recorded

Besides emotional fainting there are other causes as for example anoxia Schneider (1918) found that subjects rendered unconscious by oxygen lack fell into one of two groups non fainters and fainters ' In World War II Anderson Allen Barcroft Edholm and Manning (1946) investigated the effect upon the forearm blood flow of breathing oxygen nitrogen mixtures calculated to provide oxygen tensions equivalent to heights of between 18 000 and 24 000 feet At

the time consciousness was lost the circulation of four fifths of the subjects was in the hyperdynamic state their carotids were pulsating vigorously and there was tachycardia and increased arterial blood pressure they corresponded to Schneider s non fainters However about one fifth the fainters had typical vaso vagal syndromes including

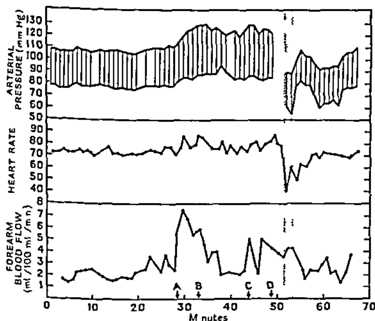


Fig 1 Experim nt h wing th t sod l tati n n m iscl o rs in fa nting r duced by emot n
Circulat ry changes luring em t onal faint t wat l s p eparati
B watcl es v nopuncture *C* nee lle int arm *D* l nks ml of l lood
Th st ppl ng repre ents los of onsci u n
In sp te of th ext ns ve fall r the l l l pre s re lur g the fa t the f rearm l loo l flow rema ne l l ated gn ly g m iscl as l lat n
(G enf ld 19 1)

increase in forearm blood flow (Fig 12 3) Brigden Howarth and Sharpey Schafer (19 ›0) recorded increases in forearm blood flow in faints induced by tilting spinal anaesthesia and other means They concluded that muscle vasodilatation was an essential part of the vaso vagal syndrome

Another important question is whether the fall in blood pressure is entirely due to vasodilatation in muscle or whether

vasodilatation elsewhere is partly responsible Fortunately we now know what happens in the circulation through the liver kidneys and brain The effect on the liver blood flow was studied by Bearn Billing Edholm and Sherlock (1951) in eight

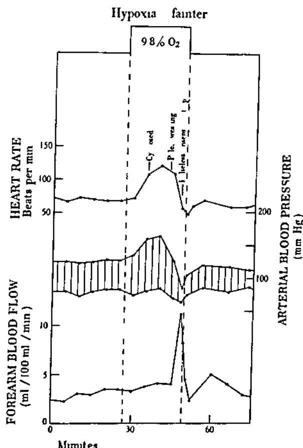


Fig 12 3 Results showing that vaso dilatation in muscle occurred in faint induced by breathing 9 8 per cent O_2 (Anderson Allen Barcroft Edholm and Manning 1946)

subjects The liver flow was measured by the bromsulphalein (BSP) method (Bradley et al 1945) The principle of this is as described in Chapter 9 Bearn et al s results show that during fainting hepatic blood flow decreased on the average to about half its normal rate As the decrease in the blood pressure was relatively more there is probably some vaso

dilatation in the splanchnic area Grayson and Swan (1950) showed by a qualitative method decrease in blood flow in fainting in the colonic mucosa de Wardener and McSwiney (1951) studied the renal blood flow by observations on the clearance of para aminohippuric acid (PAH) During the faint kidney blood flow decreased on the average to about three quarters of its normal rate As in the case of the liver there was a relatively greater decrease of arterial blood pressure and probably some renal vasodilatation

Lennox Gibbs and Gibbs (1935) studied the cerebral circulation by two methods The first was by means of a heated thermojunction placed in the internal jugular vein the temperature of the junction being an inverse function of the rate of the blood flow The second by measurement of the oxygen saturation of the internal jugular venous blood The results of both methods leave no doubt that the cerebral flow decreases during the faint

To return to the question of the extent to which the blood pressure fall in vaso vagal attacks is attributable to vasodilatation in muscle The circulation through the liver kidneys skeletal muscles and brain accounts for about four fifths of the total cardiac output During the faint the flow through the muscles is doubled but that through the other principal organs is decreased The vasodilatation in muscles is far greater than that elsewhere In as much as vasodilatation does take place in the splanchnic area and kidneys it must be in part accountable for the blood pressure fall

It is worth considering whether dilatation in the coronaries could contribute significantly to the fall in peripheral resistance The resting flow amounts only to about 200 ml a minute (from Bing et al 1949) but in exercise it may be 2 litres (Hill 1926) It has not been measured in the faint It seems unlikely that there would be much vasodilatation Probably the most important factor controlling the coronary flow is the metabolism of the heart Since in the faint heart rate and arterial blood pressure are decreased so very likely are cardiac metabolism and coronary flow Electrocardiographs taken during the syndrome show no sign of anoxia of the heart muscle (Weiss et al 1937)

Vasodilatation in another small part of the peripheral

vascular system the finger tips was recorded plethysmographically by Rushmer (1944) As the skin in the faint is pale and the blood flow in the hand diminished (Chapter 2) this may signify some release of constrictor tone in the abundant arteriovenous anastomoses in the finger tips

Some further points are of interest As the sympathetic nervous system mediates the vasodilatation in skeletal muscle (Chapter 2) it probably does so in the splanchnic area and kidneys The corollary of this is that there should be no vasodilatation or fall in blood pressure in faints in totally sympathectomized subjects In fact totally sympathectomized subjects are very apt to faint when they stand upright The cause of these 'faints' needs further investigation maybe the hypotension is due to pooling of blood in the lower part of the body and consequent decrease of right auricular pressure and cardiac output which cannot be compensated for by splanchnic vasoconstriction

Recent work suggests that hormones may play a part in the changes occurring in fainting Brun Knudsen and Raaschou (1945) noticed that the vaso vagal attacks induced by tilting were followed by pronounced oliguria They suggested that the cause was secretion of antidiuretic hormone by the pituitary This was upheld by certain experiments Diuresis in a waterloaded normal subject was inhibited by blood transfusion from one in the postsyncopal state The changes in the chloride in the urine resembled those found after injection of pituitary extract and postsyncopal oliguria was much less in two patients suffering from diabetes insipidus Taylor and Noble (1950) recovered from postsyncopal urine a posterior pituitary like antidiuretic substance Stead Kunkel and Weiss (1939) and Sunahara Duncanson and Edholm (1949) found that injection of posterior pituitary extract in normal subjects caused nausea abdominal discomfort ashen pallor and headache Pitressin secretion in the faint probably explains the persistence of pallor and splanchnic vasoconstriction for so long after the return of the blood pressure to normal (Bearn et al 1951) The possibility of suprarenal secretion must be considered too since it might explain the output of liver glucose and muscle lactic acid (Bearn et al) Now that a method of urine analysis is available for detecting increase in

blood catechol derivatives it would be interesting to apply it to postsyncopal urine (Euler and Hellner 1950)

How is fainting caused? Lewis (1932) noted the resemblance of the vaso vagal changes to those of carotid sinus stimulation in animals (Heymans and Bouckaert 1928) and in sensitive human beings (Danielopolu 1929 see also Weiss and Baker 1933) He thought that they were caused by the same centres in the brain excited by the higher centres or by unknown afferent paths Weiss Wilkins and Haynes (1937) thought that vaso vagal attacks caused by nitrite and tilting were due to cerebral anoxia but this cannot be so Breathing nitrogen (Lennox Gibbs and Gibbs 1935) or air diluted with nitrogen (Anderson et al 1946) so as deliberately to produce anoxia of the brain beyond the point of unconsciousness does not as a rule cause fainting How does nitrite and tilting induce fainting? Brigden Howarth and Sharpey Schafer (1950) have shown that tilting lowers the right auricular pressure Lowering of the right auricular pressure is caused by other procedures which induce fainting For example by haemorrhage (Brigden et al) spinal anaesthesia (Brigden et al) the post exertional state (Mateeff 1935 Eichna Horvath and Bean 1947) and by forcible compression of the chest during full inspiration followed by sudden release (Lennox et al 1935) In these cases fainting is probably induced as Sharpey Schafer once suggested by stimulation of unknown sensory receptors in the cardio pulmonary system or great veins Recent work by Pearce and Whitteridge (1951) and by Dawes and Mott (1950) emphasizes the possibility of a reflex from these areas

It is not yet known whether pituitary secretion precedes the onset of fainting If so it may help to precipitate the faint Stead Kunkel and Weiss (1939) found that intramuscular injection of pitressin induced fainting in two out of six subjects in the upright position They thought that it caused pooling of blood in the lower part of the body Rutherford Godfrey and Griffiths (1941) have since found that pitressin decreases the circulating blood volume These remarks on the cause of fainting show that it is still far from being understood

Lennox Gibbs and Gibbs (1935) were interested in the question of why fainters lose consciousness They noticed as did

Weiss and Baker (1933) that pressure on the carotid sinus sometimes caused loss of consciousness but no fall in blood pressure The loss of consciousness was caused by a neural mechanism They wondered whether in fainting loss of consciousness was due to fall in blood pressure and cerebral anoxia They found that during the faint the oxygen saturation of the arterial blood was almost normal 92 per cent but that of the internal jugular venous blood was only 20 per cent (normally 56 per cent) This was explained by the decreased cerebral blood flow As reduction of the internal jugular venous oxygen saturation to below 30 per cent by breathing nitrogen invariably caused unconsciousness they thought that unconsciousness during the vaso vagal syndrome was usually caused by anoxia However they could not say whether it was due to the direct effect of anoxia on the cells responsible for the conscious state or to stimulation of a neural mechanism

It remains to draw attention to some other vascular conditions remarkably like fainting

The first of these is the action of apomorphine reported from Innsbruck in a series of papers by Jarisch and his colleagues (Cowin 1943 Gsell 1943 Wothe 1943 Schneider 1943 Ehlich and Wallisch 1943 Bertolini and Jarisch 1944 Seidel 1945 Jarisch 1948) Subcutaneous injections of 10 mg cause lassitude yawning sweating salivation extreme pallor nausea vomiting and often unconsciousness Defaecation occurs occasionally Breathing is not affected Tachycardia is soon followed by marked bradycardia and precipitate fall in blood pressure as shown in *Fig* 12 4

Jarisch and his colleagues thought that the blood pressure fall was due to peripheral vasodilatation as it persisted after restoration of the heart rate by atropine There were signs of vasodilatation Though the skin was deadly pale the hands were warm and digital temperature often rose conspicuously owing they thought to dilatation of the A V anastomoses The oxygen saturation of the brachial venous blood was increased and it sometimes became bright red They recalled John Hunter s observation on the lady who fainted during blood letting Owing to the resemblance of the changes to those of carotid sinus and depressor nerve stimulation they thought that the dilatation was mainly in the hepatic and

splenic blood reservoirs (Koch 1931) and in the skeletal muscles (Jarisch 1925)

Examination of the electrocardiogram of these subjects showed no impairment of the heart

They thought that the apomorphine acted directly by stimulation first of the sympathetic and then of the parasympathetic centre As unconsciousness sometimes supervened when the blood pressure was normal they believed it excited Hess s

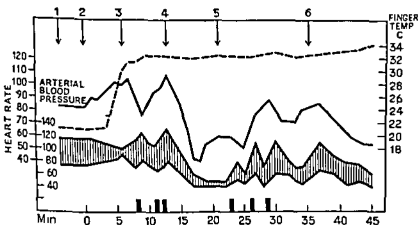


Fig 1 4 Experiment showing the likene s of the eff ts of apomorphine to those of the vaso vagal ynd om
Th i bra ly ar l a pre ip tate fall in blo l pre s re an l va o l latation in mus le as shown by a n th xyg n s turation of the venous blood from th arm vein
1 Oxyg n atu at on pe ent 10 mg apomorphin 3 Yawning feeling of fatigue 4 and 5 Oxyg n saturati n 49 an l 50 per cent resp ct ively Vom ting is lenote l by th sol l rect ngle (Ehl k and Wäll sch 1943)

(1920) sleeping centre As yet there have been no measurements of cardiac output forearm blood flow or urinary antidiuretic substance after apomorphine

Vaso vagal attacks very like faints occur in the anaesthetized cat Jarisch (1941) noticed that every now and again at the beginning of an experiment the blood pressure fell spontaneously and abruptly to about half its initial value and at the same time the heart slowed Recovery usually occurred in a few minutes Altogether he recorded 41 attacks which occurred in 10 per cent of his experiments They took place

during chloralosepernocton but not during ether or urethane anaesthesia or in decerebrate animals They invariably happened in the first ten minutes of an experiment and never except in one cat more than once They seemed to be related to the entry into the circulation of sodium citrate during the preparation for recording the blood pressure with the mercury manometer The fall in blood pressure was not abolished by atropine The pulmonary arterial pressure *fell* superior vena caval and right ventricular pressures remained constant or rose the volume of the spleen increased The phenomenon

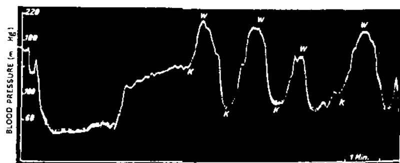


Fig 12 5 Precipitate fall in arterial blood pressure recorded by Jarisch during a vaso vagal syndrome in the chloraloséd cat
Since the vaso vagal phenomena were abolished by cooling the vagi they were believed to have been triggered by afferent sensory impulses from the heart
K vag cooled W warmed (Jarisch 1941)

reminded Jarisch of the Bezold effect (Jarisch 1940) He thought that the blood pressure fall and bradycardia might be due to excitation by the sodium citrate in susceptible cats of sensory receptors in the heart In the Bezold effect cooling the vagi abolishes the fall in pressure and bradycardia due to stimulation of these receptors by veratrine Cooling the vagi in these vaso vagal attacks also usually terminated the attack This is shown in Fig 12 5 In one case the attack persisted due to continued spontaneous activity of the centres

Konzett and Rothlin (1951) have confirmed Jarisch s observations and recorded decreases in *the volumes of the* gut and kidney They added the very interesting observation that intravenous injections of adrenaline sometimes induce vaso vagal attacks by stimulation of the Bezold receptors

REFERENCES

Anderson D P Allen W J Barcroft H Edholm O G and Manning C W (1946) *J Physiol* **104** 496

Barcroft H Edholm O G McMichael J and Sharpey Schafer E P (1944) *Lancet* **1** 489

Bearn A G Billing B Edholm O G and Sherlock S (1951) *J Physiol* **115** 442

Bertolini W and Jarisch A (1944) *Arch exp Path Pharmak* **203** 93

Bing R J Hammond M M Handelsmanff J C Powers S R Spencer F C Eckenhoff J L Goodale W T Hafkenschiel J H and Ketty S S (1949) *Amer Heart J* **38** 1

Bradley S E Ingelfinger F J Bradley G P and Curry J J (1945) *J clin Invest* **24** 890

Brigden W Howarth S and Sharpey Schafer E P (1950) *Clin Sci* **9** 79

Brun C Knudsen E O E and Raaschou F (1945) *Acta med Scand* **122** 486

Cotton T F and Lewis T (1918) *Heart* **7** 23

Danielopolu D Aslan A Maxim M Proca C G and Marcu I (1929) *Wien Arch f inn Med* **17** 381

Dawes G S and Mott J C (1950) *Brit J Pharmacol* **5** [illegible]

Ehlich W and Wallisch R (1943) *Z KreislForsch* **35** 675

Fichna L W Horvath S M and Bean W B (1947) *Amer J med Sci* **213** 641

Ershler I Kossman C L and White M S (1943) *Amer J Physiol* **138** 593

Euler U S von and Hillner S (1950) *Acta physiol Scand*

Foster M (1888) *Textbook of Physiology* I

Gowin H J (1943) *Z KreislForsch* **35** 225

Grayson J and Swan H J C (1951) *J Physiol* **112** 441

Greenfield A D M (1951) *Lancet* **1** 1302

Gsell M (1943) *Z KreislForsch* **35** 239

Hess W R (1929) *Arch Psychiat* **88** 813

Heymans C and Bouckaert J J (1928) *C R Soc Biol Paris* **99** 1871

Hill A V (1926) *Muscular Activity* Baltimore Williams and Wilkins 108

Hunter J (1793) *Works of John Hunter* edited by J F Palmer London 1837 III

Jarisch A (1925) *J Physiol* **60** 410

—— (1940) *Arch KreislForsch* **7** 260

—— (1941) *Z KreislForsch* **33** 267

—— (1948) *Klin Med Wien* **3** 956

Koch E (1931) *Die reflektorische Selbststeuerung des Kreislaufes* Dresden

Konzett H and Rothlin E (1951) *Z KreislForsch* **40** 193

Lennox W G Gibb F A and Gibbs E L (1935) *Arch Neurol Psychiat Chicago* **34** 1001

Lewis T (1932) *Brit med J* **1** 873

McDowall R J S (1938) *The Control of the Circulation of the Bl* London Longmans

Mateeff D (1935) *Arbeitsphysiologie* **8** 595
Pearce J W and Whitteridge D (1951) *Quart J exp Physiol* **36** 177
Rushmer R F (1944) *Amer J Physiol* **141** 722
Rutherford R B Godfrey I W and Griffiths J (1941) *Amer J Physiol* **134** 808
Schneider F C (1918) *J Amer med Ass* **71** 1384
Schneider G (1943) *Z KreislForsch* **35** 636
Seidel H H (1943) *Dtsch Z Nervenheilk* **157** 148
Stead E A Kunkel P and Weiss S (1939) *J clin Invest* **18** 673
Sunahara F Duncanson D and Edholm O G (1949) *Fed Proc* **8** 152
Taylor N B G and Noble R L (1950) *Proc Soc exp Biol N Y* **73** 207
Wardener H L de and McSwiney R R (1951) *Clin Sci* **10** 209
Warren J V Brannon E S Stead E A and Merrill A J (1945) *J clin Invest* **24** 337
Weiss S and Baker J P (1933) *Medicine* **12** 297
Weiss S Wilkins R W and Haynes F W (1937) *J clin Invest* **16** 73
Wilkins R W Haynes F W and Weiss S (1937) *J clin Invest* **16** 85
Wood E H and Burchell H B (1950) Personal communication
Wothe K (1943) *Z KreislForsch* **35** 235

APPENDIX

PLETHYSMOGRAPHY

This appendix is intended for those who are unfamiliar with the plethysmographic method and is divided into two parts. A few historical notes form the first part; the second contains a short general description of the experimental procedure.

Historical Notes

Apparatus for determining a change in the volume of an organ was in use in the seventeenth century. Borelli held the view that during contraction a muscle became inflated. Francis Glisson (1677) confronted this with a single experiment. In his book *de Ventriculo* he says:

"But indeed this explosion and inflation of spirits has now for some time past been silenced, convicted by the following experiment. Take an oblong glass tube of suitable capacity and shape. Fit into the top of its side near its mouth another small tube like a funnel. Let a strong muscular man insert into the mouth of the larger tube the whole of his bared arm, and secure the mouth of the tube all round to the humerus with bandages so that no water can escape from the tube. Then pour water through the funnel until the whole of the larger tube is completely filled and some water rises up into the funnel. This being done, now tell the man alternately to contract powerfully and to relax the muscles of his arm. It will be seen that when the muscles are contracted the water in the tube of the funnel sinks, rising again when relaxation takes place. From which it is clear that muscles are not inflated or swollen at the time that they are contracting, but on the contrary are lessened, shrunk and subsided. For if they were inflated the water in the tubule so far from sinking would rise. From this therefore we may infer that the fibres are shortened by an intrinsic vital movement and have no need of any abundant afflux of spirits either animal or vital by which they are inflated and being so shortened carry out the movements ordered by the brain."

Some ingenious experiments leading Jan Swammerdam to the same conclusion are shown in Fig. Ap 1 (Johnston, 1940).

In 1828 Poiseuille applied the principle to the study of the circulation. He was interested in the change in diameter of an artery caused by the heart beat. This he was able to measure by observing

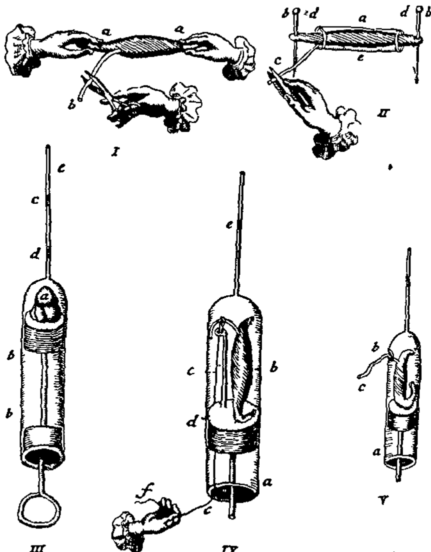


Fig Ap 1 A reproduction from Boerhaave's *Biblia Naturae* showing illustrations of the plethysmographs used by Jan Swammerdam

The text is a literal translation from part of the original text to this figure I Muscle movement in the frog *aa* the 2 muscle tendons grasped by the fingers *b* when the hanging nerve is touched the muscle contraction draws the 2 hands together II Method showing thickening of muscle during contraction *a* glass tube through which muscle is drawn *bb* needle transpiercing tendons c the nerve touched *dd* displacement of needle *bb* *e* contracting muscle fills up centre of glass tube III Method showing that the heart occupies less space in contraction *a* contracting heart is placed upon piston of glass tube *bb* glass tube *c* water droplet introduced into tube of siphon descends with heart contraction *d* place in tube showing distance moved by droplet during time of descent IV Method showing that contracted muscle takes up less space *a* tube *b* muscle *c* silver thread through loop of which the nerve is passed *d* copper thread with loop at top through which silver thread is drawn *e* water droplet in siphon tube *f* hand stimulating nerve muscle contracts and droplet descends a little V Another method of showing the above *a* glass siphon *b* aperture drilled in the siphon c nerve drawn through the aperture (Johnston 1940)

the movements of a column of water in a graduated vertical glass tube communicating with a watertight chamber which contained a segment of a large artery

The same principle was employed by Piégu in 1846 and independently *by Chelius in 1850 to study circulatory and respiratory* volume changes in the human limbs The first instrument to record volume changes graphically which could therefore be truly said to have been a plethysmograph (πληθισμός a filling and γράφειν I record) was described by Buisson in 1862 Details of the well known Mosso plethysmograph in use in 1875 are shown in Fig Ap 2 (Luciani 1911)

In 1905 Brodie and Russell discovered that the plethysmograph could be used to determine the rate of the blood flow through an organ This discovery had such far reaching results that it is best described in the authors own words Brodie and Russell say

Most valuable information is to be gained by the plethysmograph as ordinarily applied but it gives only qualitative results which *moreover in many cases are difficult to interpret During the past* three years we have applied a simple modification to the plethysmographic method which enables us to determine the rate of flow quantitatively with considerable accuracy In principle this consists of blocking the vein of an organ enclosed within the plethysmograph for a short interval of time The whole of the venous blood is thus retained in the plethysmograph and leads to a rise of the lever of the recorder If the recorder be calibrated the rate at which the lever rises enables us to determine the rate of blood flow into the vein In applying such a method as this it is obviously essential that the blockage of the vein must not be maintained so long as to impede the flow through the capillaries Under all ordinary conditions the veins are never completely filled so that it is possible to store up in them a small extra quantity of blood without checking the inflow into them from the capillaries [omission]

The danger that the artificial venous obstruction may be checking the capillary inflow is easily guarded against by noting whether the lever of the recorder continues to rise at a uniform rate during the whole period of observation Should this not be the case but the tracing become concave to the zero abscissa line the clamping is being maintained too long a time and the observation must be discarded

We have controlled the method by comparing it with observations upon the rate of venous outflow as conducted in the experiments of Barcroft and Brodie upon the kidney the only modifications we have introduced being to record the rate of flow

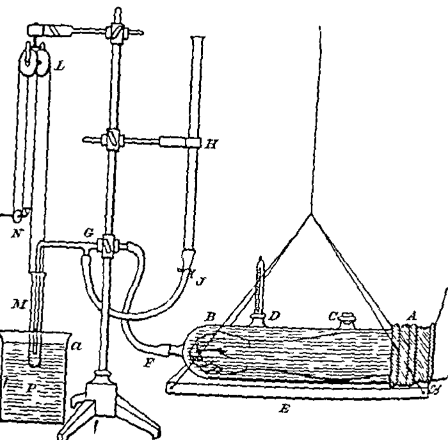


Fig Ap 9 Mosso's plethysmograph for recording slow variations in volume of vessels of forearm (diagram)

A B glass cylinder to receive the forearm closed by rubber band this *rests on the board E* which is suspended from the ceiling by a wire *C* opening closed with a cork through which the cylinder can be filled with *lukewarm water D* opening through which a thermometer is passed showing temperature of water *F G* tube through which the cylinder containing *the forearm* communicates with the small cylinder *M* which floats above the level of the fluid *a b* contained in large vessel *P N* lead weight carrying *the pen to write on moving cylinder of kymograph* which counterpoises *M* with which it is connected by two silk threads passing over the double pulleys *L H J* burette that can be raised or lowered in adding or changing the water in the float The instrument works as follows when the vessels of the forearm contract an amount of water corresponding with the diminution in volume is aspirated from the float *M* to the cylinder *A B* this raises the float and depresses the counterpoise *N* which records the diminution of volume on the revolving cylinder When on the contrary the vessels of the forearm dilate a quantity of water in the cylinder *A B* is driven out into *M* so that it sinks and *N* is raised recording the increase of volume To avoid positive or negative pressure above the forearm immersed in the cylinder *A B* care must be taken that its upper level is at the same level *a b* as the water contained in the receiver *P* where *M* is floating (Luciani 1911)

from the vein instead of timing it by a stop watch. We have found that the two methods give nearly identical results.

The method is applicable to all organs which can be inserted into an oncometer provided that the vein can be clamped within the oncometer. It is also applicable to a limb for the venous outflow can be blocked there by a circular ligature applied with so much



Fig. Ap 3. Thomas Gregor Brodie F R S.
The original was kindly loaned by the Royal Society

force as to compress the veins without interfering with the arterial inflow.

In 1905 Brodie held no fewer than three posts in London: Professor Superintendent at the Brown Institution, Professor of Physiology at the Royal Veterinary College, and Lecturer in Physiology at the London School of Medicine for Women. His portrait is shown in Fig. Ap 3. It is not clear where he and Russell

performed the experiments referred to in their paper Nor is it known whether they actually recorded the rate of the blood flow in a human limb though their words suggest that they did so

Brodie and Russell's remark that the plethysmograph could be used to determine the blood flow in a human limb was followed up by Hewlett and van Zwaluwenburg in 1909 The hand forearm and elbow were enclosed in their instrument Compression of the veins without interference with the arterial inflow was achieved by the use of a narrow pneumatic cuff placed on the upper arm Their observations were made with the plethysmograph filled with air and they *noted that the rate of the circulation was profoundly* affected by fluctuations in the temperature

To avoid errors due to temperature fluctuations and those due to movements of the limb in and out of the Mosso type of plethysmograph used by Hewlett and van Zwaluwenburg Lewis and Grant in 1925 devised the type of plethysmograph shown in Fig Ap 4 It enclosed a segment of the forearm and contained water to maintain the temperature constant

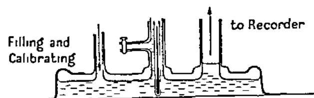
The first plethysmograph to be used for the determination of the rate of the blood flow in the hand was described by Freeman (1935) A simple form of hand plethysmograph is shown in Fig Ap 5

Three years later Grant and Pearson (1938) showed that what was measured by the hand plethysmograph was for the most part the circulation through the skin and what was measured by the forearm plethysmograph was mainly the blood flow through the skeletal muscles The value of the plethysmograph for the determination of muscle blood flow was improved by placing it on the upper fleshy part of the forearm and by arresting the circulation at the wrist to prevent the entry of venous blood returning from the hand

Experimental Procedure

This may conveniently be described by considering an experiment in which the effect of some procedure is to be tested on the rate of the circulation in the right hand and in the left forearm

Room temperature is kept constant at 20 C ∓ 1 and entry of persons during the experiment is discouraged Fig Ap 6 shows a general view of the subject and plethysmographs The subject is on a comfortable rubber mattress on a narrow table his head supported and his body covered with a single blanket The left hand is covered with a rubber surgical glove (Kerslake 1949) several sizes too large which is stuck round the wrist to the edge of a hole in a ¼ in thick soft rubber diaphragm The diaphragm fits the wrist snugly—but not tightly for venous congestion must be



ARM

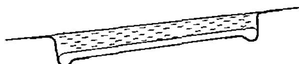
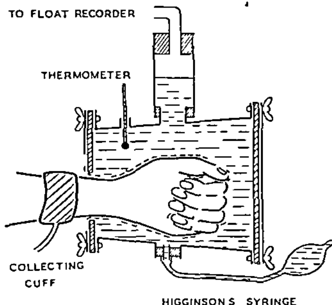


Fig Ap 4 Lew a d Grant pl tl ysmograph for the forearm



F g Ap A s mpl form of pl thysmograph for the hand
The h n l en losed n a loose f tt ng surgi al rubber glove (R F Whelan M D Thes Belfast)

avoided By means of wing nuts and two semicircular metal plates the periphery of the diaphragm is bolted firmly to a 2 in wide flange on the end of the plethysmograph The plethysmograph contains water up to the lower part of the vertical glass tube The weight of the water presses the glove everywhere against the hand From time to time the water is agitated by squeezing a bulb communicating with the interior of the plethysmograph and its exterior is heated with a small flame to keep the temperature at 32 C The plethysmograph is mounted on a retort stand placed on a small table beside the subject its height is such as to ensure that the veins of



Fig Ap 6 Photograph showing plethysmographs on the right hand and the left forearm

the hand are collapsed (Cooper Cross Greenfield Hamilton and Scarborough 1949) The elbow is slightly bent to prevent the communication of respiratory movements to the hand and rests on a comfortable pillow A narrow pneumatic cuff surrounds the wrist and is held lightly but firmly in position by a crepe bandage

The same principles apply to the plethysmograph on the other arm The upper part of the forearm is covered with a loose sleeve (Krogh Landis and Turner 1932 Grant and Pearson 1938) of thin latex rubber fixed at each end round a suitably shaped central hole in a soft rubber diaphragm The temperature of the water for the forearm is kept at 34-35 C (Barcroft and Edholm 1943,

1940) The collecting cuff is placed just above the elbow and the arresting cuff on the wrist. Both are held in position by crepe bandages. (This is a convenient point to note that a more even constant temperature is maintained in electrically heated thermo-

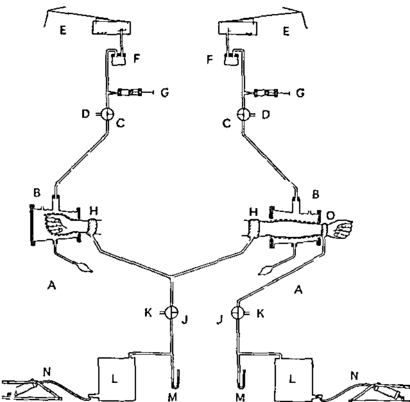


Fig. Ap 7. Diagram of apparatus for recording the rate of arterial inflow into the right hand and left forearm.
AA, plethysmographs (thermometers not shown); *BB*, vertical glass tubes; *CC*, three-way glass taps; *DD*, side tubes communicating with room air; *EE*, float recorders; *FF*, traps; *GG*, syringes; *HH O*, pneumatic cuffs; *JJ*, three-way glass taps; *KK*, side tubes communicating with room air; *LL*, reservoirs for compressed air; *MM*, mercury manometer; *NN*, foot pump.

statically controlled plethysmographs which on the other hand are more bulky and must be very carefully made to avoid danger of electrocution (Abramson 1944).)

The recording apparatus and arrangements for inflating the cuffs are shown diagrammatically in Fig. Ap 7. Each plethysmograph

A A is connected through a vertical glass tube B B to a wide bore three way glass tap C C by means of which it can be put in communication with the room through a side tube D D or with a float recorder E E Reflux of water from the recorder into the tubing is prevented by a small trap F F The level of the writing point can be adjusted by means of a syringe G G The two collecting cuffs H H are connected to a wide bore three way tap J by means of which they can be put in communication with the room through the side tube K or with a reservoir of compressed air L The pressure of the air is shown by a mercury manometer M and maintained at 60–70 mm Hg by a foot pump N The arresting cuff O is connected to a second similar set of apparatus J K L M N with the difference that the air in the reservoir L is maintained at a pressure of 200 mm Hg

All four taps C C J J and both syringes C G are mounted on a board on the kymograph table with the foot pump readily accessible below Before beginning recording the writing points are adjusted one above the other on the smoked kymograph paper and horizontal base lines are drawn round the paper

To obtain simultaneous tracings of the rates of the arterial inflow into the hand and into the forearm the procedure is as follows The air pressure in the reservoirs is checked The taps are turned to put the plethysmographs in communication with the recorders As the recorders are apt to stick when empty some air is introduced by means of the syringes so that the writing points are raised a little above the base lines Tap K is then turned to arrest the circulation distal to the forearm plethysmograph Three quarters of a minute later the kymograph is started the switch also turns on a light illuminating a notice in front of the subject with the words keep quite still and look at this light One minute after arresting the circulation in the hand (Kerslake 1948 Roddie 1951) tap F is turned to inflate both collecting cuffs simultaneously The water level in the vertical glass tubes begins to rise air is displaced into the recorders and the arterial inflow curves are inscribed After 10 sec of venous compression the kymograph is stopped and the taps turned to put the plethysmographs and cuffs in communication with the room air

At the beginning of the experiment tracings of the arterial inflow are generally recorded at 5 min intervals for ½ or ¾ an hour to confirm that the circulation has reached a steady state The effect of some procedure is then tested If a rapid alteration in the rate of the circulation is anticipated inflow curves may be recorded at more frequent intervals For this purpose the collecting pressure is applied for about 5 sec at the beginning of each ½ or ¼ min

interval the circulation in the hand remaining arrested and the drum continuing in motion

*At the end of the experiment each recorder is calibrated by intro*ducing a known volume of air into the system with the syringe The distance travelled by the recording paper in 1 min is marked

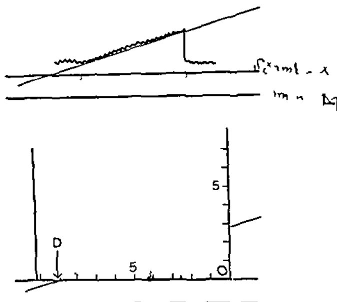


Fig Ap 8 P ocedure for calculating the rate of tl e blood flow from the trac ng

Top Inflow curve with sloping line drawn an l continue l through ho zontal ba e line

B ttom Use of graph pape uled n cent metres and mill metres to read off the rate of the blo l flow directly in ml /100 ml limb/m n Lower edge of pape on base l ne w th mark *D* at point of intersection of sloping lin Cent metre scal up ight hand s de Sloping l n ntersects at J cm wh ch is al o th ate of the l lood fl w n ml /100 ml tis ue/min

upon it and the volumes of the *portions of the hand and* forearm enclosed in the plethysmographs measured by water displacement

The rates of the blood flow are then calculated from the curves traced on the kymograph paper Sloping lines are *drawn through* the inflow curves to cut the base line as shown in Fig Ap 8 The experiment constant *D* is obtained from formula

$$D = \frac{V}{dl}$$

where L is the vertical distance travelled by the recorder writing point for 1 ml increment of content

V is the volume of the hand in hundreds of millilitres

M is the distance in centimetres travelled by the kymograph paper in 1 min

A piece of graph paper ruled in centimetres and millimetres is trimmed square and a mark made at the bottom edge D cm from the right hand corner as shown in Fig Ap 8 A centimetre scale is marked along the edge of the right hand side with the zero at the right hand bottom corner The rates of the blood flow are now read off the kymograph paper The graph paper is placed with the bottom edge touching the horizontal base line the mark D coinciding with the point where the base line is intersected by a sloping line The distance from the right hand bottom corner of the graph paper up the right hand side to the point of intersection of this sloping line is read off on the centimetre scale The figure obtained is that for the rate of the blood flow expressed in millilitres per 100 ml hand per minute The rates of blood flow in the hand are read off from the other inflow curves in a similar way To obtain those for the forearm the values of L and V being different a new value of D must first be found from the formula—

The method has the advantage that once the value of D has been obtained the rates of the blood flow for all the inflow curves for a part can be quickly read off without any further arithmetic The basis for this graphic method is as follows

Let L M and V be defined as above

D be any given distance in centimetres travelled by the drum paper

I be the upward movement of the writing point in centimetres while the paper goes D cm

F be the rate of the blood flow in ml 100 ml tissue/min

Then

$$F = \frac{LM}{VDI} \qquad 1$$

In any given experiment L M and V are constant A distance D can therefore be chosen so that

$$D = \frac{M}{VI}$$

Substituting this in equation 1

$$F = \frac{LM}{VI} \times \frac{VI}{M}$$

or

$$F = L$$

That is the rate of the blood flow in ml/100 ml tissue/min is equal to the upward movement of the writing point in centimetres

Similar principles apply to the method of measuring the rates of the blood flow in the calf of the leg and in the foot

REFERENCES

Abramson D I (1944) *Vascular Responses in the Extremities of Man in Health and Disease* Chicago University of Chicago Press

Barcroft H and Edholm O G (1943) *J Physiol* **102** 5

—— (1946) *J Physiol* **104** 366

Brodie T G and Russell A E (1905) *J Physiol* **32** xlvii

Cooper K E Cross K W Greenfield A D M Hamilton D McK and Scarborough A (1949) *Clin Sci* **8** 217

Freeman N F (1935) *Amer J Physiol* **113** 384

Glisson Francis (1677) *Tractatus de ventriculo et intestinis* Quoted from Michael Foster [1901] *Lectures on the History of Physiology* page 290 Cambridge University Press

Grant R T and Pearson R S B (1938) *Clin Sci* **3** 119

Hewlett A W and Zwaluwenburg J G van (1909) *Heart* **1** 87

Johnston C A (1940) *Surg Gynec Obstet* **70** 31

Kerslake D McK (1948) *J Physiol* **107** 43P

—— (1949) Ph D Thesis London University

Krogh A Landis E M and Turner A H (1932) *J clin Invest* **11** 63

Lewis T and Grant R T (1925) *Heart* **12** 73

Luciani L (1911) *Human Physiology* Translated by F A Welby London Macmillan

Roddie I C (1951) *J Physiol* **112** 204

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